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(54) Title: LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY, MUTATIONS THEREOF AND METHOD USING SAME TO ASSESS, DIAGNOSE, PROGNOSIS OR TREAT EPILEPSY

(57) Abstract: The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three genes mapping to chromosome 2, which show mutations in patients with epilepsy. The invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA) and to the use thereof to assess, diagnose, prognosis or treat epilepsy, to predict an epileptic individual's response to medication and to identify agents which modulate the function of the SCNA. The invention provides screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders. In a particular embodiment, the invention provides a method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising: providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting this screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene; wherein a test compound which modulates the biological activity thereof is a compound with the desired therapeutic effect.

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TITLE OF THE INVENTION

LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY,
MUTATIONS THEREOF AND METHOD USING SAME TO ASSESS,
DIAGNOSE, PROGNOSE OR TREAT EPILEPSY

5 FIELD OF THE INVENTION

The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three loci mapping to chromosome 2, which show a linkage with epilepsy in patients. The
10 invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA), to variations and mutations in these sequences and to the use thereof to assess, diagnose, prognose or treat epilepsy. The invention also provides screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for
15 epilepsy and related neurological disorders.

BACKGROUND OF THE INVENTION

Epilepsy is one of the most common neurological conditions, occurring in about 1.0% of the general population. The disease is characterised by paroxysmal abnormal electrical discharges in
20 the brain, which lead to transient cerebral dysfunction in the form of a seizure. A seizure is considered partial when the epileptic discharge is limited to part of one brain hemisphere, or generalised when it involves both cerebral hemispheres at the onset. The current classification of the epileptic syndromes rests on two criteria: 1) seizure type which may be
25 generalised or partial at the onset, according to clinical and EEG features; and 2) etiology, which may be idiopathic, cryptogenic and symptomatic. Symptomatic epilepsies have multiple and heterogeneous causes including

brain injury, CNS infection, migrational and metabolic disorders. In the majority (65%) of the patients with either generalised or partial epilepsy, there is no underlying cause (idiopathic) or the cause is thought to be hidden or occult (cryptogenic). Also, in the idiopathic epileptic syndromes, there is no evidence of cerebral dysfunction other than the seizure, and the neurological examination is normal. There is now increasing evidence that in this latter group, genetic factors are important, especially for the idiopathic generalised epilepsy (IGE). In a recent study, Berkovic et al (1998) showed a 62% concordance rate in monozygotic twins overall for epilepsy. In this study, a higher concordance rate has been found in the generalised compared to the partial epilepsies, with 76% concordance rate for IGE. Recent studies using molecular genetic approaches have shown that many susceptibility genes for the epilepsies in human involve membrane ion channel and related proteins. These studies include the syndrome of benign familial neonatal convulsions where two loci have been identified [EBN1 on chromosome 20, the KCNQ2 gene (a potassium channel); and EBN2 on chromosome 8, the KCNQ3 gene (also a potassium channel)] (Bievert et al, 1998; Charlier et al, 1998; Singh et al, 1998), as well as autosomal dominant nocturnal frontal lobe epilepsy [ADNFLE - chromosome 20, and the CHRNA4 gene (the neuronal nicotinic acetylcholine receptor alpha 4 subunit)] (Steinlein et al, 1995). More recently, there was a clinical description of a new syndrome (GEFS), which consisted of generalised epilepsy with febrile seizures. According to the current classification of epileptic syndrome, this syndrome would fall in the category of IGE, based on the seizure and electroencephalographic features. However, febrile seizures were present in all probands with GEFS, and the pattern of inheritance was clearly autosomal dominant, which are not part of the usual IGE phenotype. This unique GEFS syndrome has been shown to be associated with a mutation on the beta-1 subunit of brain voltage-gated sodium channel (SCN1B) gene (Wallace et

al, 1998). In addition, three different groups, including the group of the present inventors, have identified another locus on chromosome 2 in large kindred with this specific syndrome (GEFS). This region contains many candidate genes, including a cluster of alpha subunits of sodium channels (SCNA). Voltage-gated sodium channels play an important role in the generation of action potential in nerve cells and muscle. The alpha subunit (SCNA) is the main component of the channel, and would be sufficient to generate an efficient channel when expressed in cells *in vitro*. In turn, the beta-1 and 2 subunits need an alpha subunit to give an effective channel. The role of these subunits would be to modify the kinetic properties of the channel, mainly by fast inactivation of the sodium currents. The mutation found in the GEFS syndrome on the SCN1B gene was shown to reduce the fast inactivation of the sodium channels as compared to a normal SCNB1, when co-expressed with an alpha subunit. It is probable that this could be the mechanism by which the mutation induce an hyperexcitability state in the brain, leading to seizure in humans. Interestingly, the mechanism of action of most of the anticonvulsant drugs is through a reduction of the repetitive firing of neurons, which is also known to be dependent on fast inactivation. These finding make it likely that additional epilepsy genes will be identified by mutations in ion channels.

There thus remains a need to identify whether IGE is caused by a mutation in a sodium channel (SCNA). There also remains a need to assess whether a mutation(s) in SCNA is associated with GEFs. There also remains a need to determine whether a mutation that affects the fast inactivation of a sodium channel, given the particular phenotype of GEFS or IGE, could be linked to a region which includes SCNA genes.

The present invention seeks to meet these and other needs.

The present description refers to a number of documents, the content of which is herein incorporated by reference in their entirety.

5 SUMMARY OF THE INVENTION

In one embodiment, the present invention relates to a genetic assay for determining predisposition to epilepsy.

10 In another embodiment, the present invention relates to a use of at least one of the loci of the present invention or an equivalent thereof (e.g. a loci in linkage disequilibrium therewith) as a marker for epilepsy and to determine the optimal treatment thereof (e.g. to guide the treatment modalities, thereby optimizing treatment to a particular clinical situation).

15 Yet in another embodiment, the present invention relates to an assay to screen for drugs for the treatment and/or prevention of epilepsy. In a particular embodiment, such assays can be designed using cells from patients having a known genotype at one of the loci of the present invention. These cells harboring recombinant vectors can enable an assessment of the functionality of the SCN1A, and/or SCN2A and/or
20 SCN3A and a combination thereof. Non-limiting examples of assays that could be used in accordance with the present invention include *cis-trans* assays similar to those described in U.S.P. 4,981,784.

25 It shall be understood that the determination of allelic variations in at least one of the loci of the present invention can be combined to the determination of allelic variation in other gene/markers linked to a predisposition to epilepsy. This combination of genotype analyses could lead to better diagnosis programs and/or treatment of epilepsy. Non-limiting examples of such markers include SCN1B, EBN1, KCNQ2, EBN2, KCNQ3, ADFLE and CHRNA4.

In accordance with the present invention, there is therefore provided a method of determining an individual's predisposition to epilepsy, which comprises determining the genotype of at least one locus selected from the group consisting of SCN1A, SCN2A and SCN3A.

- 5 In one particular embodiment, the present invention provides a method of determining an individual's predisposition to epilepsy, which comprises determining a polymorphism (directly or indirectly by linkage disequilibrium) in a biological sample of an individual and analyzing the allelic variation in at least one of the loci selected from SCN1A, SCN2A
10 and SCN3A, thereby determining an individual's predisposition to epilepsy.

- In accordance with the present invention, there is also provided a method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological
15 disorders comprising providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting the screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene; wherein a test compound which modulates the
20 biological activity is a compound with this therapeutic effect.

- Also provided within the present invention is a compound having therapeutic effect on epilepsy or other neurological disorders, identified by a method comprising: providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A
25 protein or gene; contacting the screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene, wherein a test compound which modulates the biological activity is a compound with this therapeutic effect.

SCN1A, SCN2A and SCN3A refers to genes and proteins for Sodium Channel, Neuronal Type I, Alpha Subunit isoforms, and are described at OMIM # 182389 (Online Mendelian Inheritance in Man). These genes are structurally distinct sodium channel alpha-subunit isoforms in brain; also known as brain types I, II and III, respectively. Gene, cDNA and protein sequences for the various isoforms are shown in SEQ ID NOS:1-98.

Numerous methods for determining a genotype are known and available to the skilled artisan. All these genotype determination methods are within the scope of the present invention. In a particular embodiment of a method of the present invention, the determination of the genotype comprises an amplification of a segment of one of the loci selected from the group consisting of SCN1A, SCN2A and SCN3A and in a particularly preferred embodiment, the amplification is carried out using polymerase chain reaction.

In a particular embodiment, a pair of primers is designed to specifically amplify a segment of one of the markers of the present invention. This pair of primers is preferably derived from a nucleic acid sequence of SCN1A, SCN2A or SCN3A or from sequences flanking these genes, to amplify a segment of SCN1A, SCN2A or SCN3A (or to amplify a segment of a loci in linkage disequilibrium with at least one of the loci of the present invention). While a number of primers are exemplified herein, other primer pairs can be designed, using the sequences of the SCN1A, SCN2A and SCN3A nucleic acids molecules described hereinbelow. The same would apply to primer pairs from loci in linkage disequilibrium with the markers of the present invention.

Restriction fragment length polymorphisms can be used to determine polymorphisms at the SCN1A, SCN2A and SCN3A loci (and equivalent loci).

While human SCN1A, SCN2A and SCN3A are preferred sequences (nucleic acid and proteins) in accordance with the present invention, the invention should not be so limited. Indeed, in view of the significant conservation of these genes throughout evolution, sequences from different species, and preferably mammalian species, could be used in the assays of the present invention. One non-limiting example is the rat SCN1A ortholog gene which shows 95% identity with the human SCN1A gene. The significant conservation of the mouse SCN1A gene can also be observed in OMIM (see above).

10 In order to provide a clear and consistent understanding of terms used in the present description, a number of definitions are provided hereinbelow.

As used herein the term "RFLP" refers to restriction fragment length polymorphism.

15 The terms "polymorphism", "DNA polymorphism" and the like, refer to any sequence in the human genome which exists in more than one version or variant in the population.

The term "linkage disequilibrium" refers to any degree of non-random genetic association between one or more allele(s) of two different polymorphic DNA sequences, that is due to the physical proximity of the two loci. Linkage disequilibrium is present when two DNA segments that are very close to each other on a given chromosome will tend to remain unseparated for several generations with the consequence that alleles of a DNA polymorphism (or marker) in one segment will show a non-random association with the alleles of a different DNA polymorphism (or marker) located in the other DNA segment nearby. Hence, testing of a marker in linkage disequilibrium with the polymorphisms of the present invention at the SCN1A, SCN2A and/or SCN3A genes (indirect testing), will give almost the same information as

testing for the SCN1A, SCN2A and SCN3A polymorphisms directly. This situation is encountered throughout the human genome when two DNA polymorphisms that are very close to each other are studied. Linkage disequilibriums are well known in the art and various degrees of linkage disequilibrium can be encountered between two genetic markers so that
5 some are more closely associated than others.

It shall be recognized by the person skilled in the art to which the present invention pertains, that since some of the polymorphisms or mutations herein identified in the SCN1A, SCN2A
10 and/or SCN3A genes can be within the coding region of the genes and therefore expressed, that the present invention should not be limited to the identification of the polymorphisms/mutations at the DNA level (whether on genomic DNA, amplified DNA, cDNA, or the like). Indeed, the herein-identified polymorphisms and/or mutations could be detected at
15 the mRNA or protein level. Such detections of polymorphism identification on mRNA or protein are known in the art. Non-limiting examples include detection based on oligos designed to hybridize to mRNA or ligands such as antibodies which are specific to the encoded polymorphism (i.e. specific to the protein fragment encoded by the distinct polymorphisms).

20 Nucleotide sequences are presented herein by single strand, in the 5' to 3' direction, from left to right, using the one letter nucleotide symbols as commonly used in the art and in accordance with the recommendations of the IUPAC-IUB Biochemical Nomenclature Commission.

25 Unless defined otherwise, the scientific and technological terms and nomenclature used herein have the same meaning as commonly understood by a person of ordinary skill to which this invention pertains. Generally, the procedures for cell cultures, infection, molecular biology methods and the like are common methods

used in the art. Such standard techniques can be found in reference manuals such as for example Sambrook et al. (1989, Molecular Cloning- A Laboratory Manual, Cold Spring Harbor Laboratories) and Ausubel et al. (1994, Current Protocols in Molecular Biology, Wiley, New York).

5 The present description refers to a number of routinely used recombinant DNA (rDNA) technology terms. Nevertheless, definitions of selected examples of such rDNA terms are provided for clarity and consistency.

10 As used herein, "nucleic acid molecule", refers to a polymer of nucleotides. Non-limiting examples thereof include DNA (i.e. genomic DNA, cDNA, RNA molecules (i.e. mRNA) and chimeras of DNA and RNA. The nucleic acid molecule can be obtained by cloning techniques or synthesized. DNA can be double-stranded or single-stranded (coding strand or non-coding strand [antisense]).

15 The term "recombinant DNA" as known in the art refers to a DNA molecule resulting from the joining of DNA segments. This is often referred to as genetic engineering.

20 The term "DNA segment", is used herein, to refer to a DNA molecule comprising a linear stretch or sequence of nucleotides. This sequence when read in accordance with the genetic code, can encode a linear stretch or sequence of amino acids which can be referred to as a polypeptide, protein, protein fragment and the like.

25 The terminology "amplification pair" refers herein to a pair of oligonucleotides (oligos) of the present invention, which are selected to be used together in amplifying a selected nucleic acid sequence by one of a number of types of amplification processes, preferably a polymerase chain reaction. Other types of amplification processes include ligase chain reaction, strand displacement amplification, or nucleic acid sequence-based amplification, as explained

in greater detail below. As commonly known in the art, the oligos are designed to bind to a complementary sequence under selected conditions.

The nucleic acid (i.e. DNA, RNA or chimeras thereof)
5 for practicing the present invention may be obtained according to well known methods.

Oligonucleotide probes or primers of the present invention may be of any suitable length, depending on the particular assay format and the particular needs and targeted genomes employed.
10 In general, the oligonucleotide probes or primers are at least 12 nucleotides in length, preferably between 15 and 24 molecules, and they may be adapted to be especially suited to a chosen nucleic acid amplification system. As commonly known in the art, the oligonucleotide probes and primers can be designed by taking into consideration the
15 melting point of hybridization thereof with its targeted sequence (see below and in Sambrook et al., 1989, Molecular Cloning -A Laboratory Manual, 2nd Edition, CSH Laboratories; Ausubel et al., 1989, in Current Protocols in Molecular Biology, John Wiley & Sons Inc., N.Y.).

The term "DNA" molecule or sequence (as well as
20 sometimes the term "oligonucleotide") refers to a molecule comprised of the deoxyribonucleotides adenine (A), guanine (G), thymine (T) and/or cytosine (C). Sometimes, in a double-stranded form, it can comprise or include a "regulatory element" according to the present invention, as the term is defined herein. The term "oligonucleotide" or "DNA" can be found
25 in linear DNA molecules or fragments, viruses, plasmids, vectors, chromosomes or synthetically derived DNA. As used herein, particular double-stranded DNA sequences may be described according to the normal convention of giving only the sequence in the 5' to 3' direction. Of

course, as very well-known, DNA molecules or sequences are often in single stranded form.

“Nucleic acid hybridization” refers generally to the hybridization of two single-stranded nucleic acid molecules having complementary base sequences, which under appropriate conditions will form a thermodynamically favored double-stranded structure. Examples of hybridization conditions can be found in the two laboratory manuals referred to above (Sambrook et al., 1989, *supra* and Ausubel et al., 1989, *supra*) and are commonly known in the art. In the case of a hybridization to a nitrocellulose filter, as for example in the well known Southern blotting procedure, a nitrocellulose filter can be incubated overnight at 65°C with a labeled probe in a solution containing 50% formamide, high salt (5 x SSC or 5 x SSPE), 5 x Denhardt's solution, 1% SDS, and 100 µg/ml denatured carrier DNA (i.e. salmon sperm DNA). The non-specifically binding probe can then be washed off the filter by several washes in 0.2 x SSC/0.1% SDS at a temperature which is selected in view of the desired stringency: room temperature (low stringency), 42°C (moderate stringency) or 65°C (high stringency). The selected temperature is based on the melting temperature (T_m) of the DNA hybrid. Of course, RNA-DNA hybrids can also be formed and detected. In such cases, the conditions of hybridization and washing can be adapted according to well known methods by the person of ordinary skill. Stringent conditions will be preferably used (Sambrook et al., 1989, *supra*).

Probes of the invention can be utilized with naturally occurring sugar-phosphate backbones as well as modified backbones including phosphorothioates, dithionates, alkyl phosphonates and α -nucleotides and the like. Modified sugar-phosphate backbones are generally taught by Miller, 1988, Ann. Reports Med. Chem. 23:295 and Moran et al., 1987, Nucleic Acids Res., 14:5019. Probes of the invention

can be constructed of either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA), and preferably of DNA.

The types of detection methods in which probes can be used include Southern blots (DNA detection), dot or slot blots (DNA, RNA), and Northern blots (RNA detection). Although less preferred, labeled proteins could also be used to detect a particular nucleic acid sequence to which it binds. More recently, PNAs have been described (Nielsen et al. 1999, Current Opin. Biotechnol. 10:71-75). PNAs could also be used to detect the polymorphisms of the present invention. Other detection methods include kits containing probes on a dipstick setup and the like.

Although the present invention is not specifically dependent on the use of a label for the detection of a particular nucleic acid sequence, such a label might be beneficial, by increasing the sensitivity of the detection. Furthermore, it enables automation. Probes can be labeled according to numerous well known methods (Sambrook et al., 1989, supra). Non-limiting examples of labels include ^3H , ^{14}C , ^{32}P , and ^{35}S . Non-limiting examples of detectable markers include ligands, fluorophores, chemiluminescent agents, enzymes, and antibodies. Other detectable markers for use with probes, which can enable an increase in sensitivity of the method of the invention, include biotin and radionucleotides. It will become evident to the person of ordinary skill that the choice of a particular label dictates the manner in which it is bound to the probe.

As commonly known, radioactive nucleotides can be incorporated into probes of the invention by several methods. Non-limiting examples thereof include kinasing the 5' ends of the probes using gamma ^{32}P ATP and polynucleotide kinase, using the Klenow fragment of Pol I of *E. coli* in the presence of radioactive dNTP (i.e. uniformly labeled DNA

probe using random oligonucleotide primers in low-melt gels), using the SP6/T7 system to transcribe a DNA segment in the presence of one or more radioactive NTP, and the like.

5 As used herein, "oligonucleotides" or "oligos" define a molecule having two or more nucleotides (ribo or deoxyribonucleotides). The size of the oligo will be dictated by the particular situation and ultimately on the particular use thereof and adapted accordingly by the person of ordinary skill. An oligonucleotide can be synthesised chemically or derived by cloning according to well known methods.

10 As used herein, a "primer" defines an oligonucleotide which is capable of annealing to a target sequence, thereby creating a double stranded region which can serve as an initiation point for nucleic acid synthesis under suitable conditions.

15 Amplification of a selected, or target, nucleic acid sequence may be carried out by a number of suitable methods. See generally Kwoh et al., 1990, Am. Biotechnol. Lab. 8:14-25. Numerous amplification techniques have been described and can be readily adapted to suit particular needs of a person of ordinary skill. Non-limiting examples of amplification techniques include polymerase chain reaction (PCR),
20 ligase chain reaction (LCR), strand displacement amplification (SDA), transcription-based amplification, the Q-beta replicase system and NASBA (Kwoh et al., 1989, Proc. Natl. Acad. Sci. USA 86, 1173-1177; Lizardi et al., 1988, BioTechnology 6:1197-1202; Malek et al., 1994, Methods Mol. Biol., 28:253-260; and Sambrook et al., 1989, *supra*).
25 Preferably, amplification will be carried out using PCR.

Polymerase chain reaction (PCR) is carried out in accordance with known techniques. See, e.g., U.S. Pat. Nos. 4,683,195; 4,683,202; 4,800,159; and 4,965,188 (the disclosures of all three U.S. Patent are incorporated herein by reference). In general, PCR involves, a

treatment of a nucleic acid sample (e.g., in the presence of a heat stable DNA polymerase) under hybridizing conditions, with one oligonucleotide primer for each strand of the specific sequence to be detected. An extension product of each primer which is synthesized is complementary to each of the two nucleic acid strands, with the primers sufficiently complementary to each strand of the specific sequence to hybridize therewith. The extension product synthesized from each primer can also serve as a template for further synthesis of extension products using the same primers. Following a sufficient number of rounds of synthesis of extension products, the sample is analysed to assess whether the sequence or sequences to be detected are present. Detection of the amplified sequence may be carried out by visualization following EtBr staining of the DNA following gel electrophores, or using a detectable label in accordance with known techniques, and the like. For a review on PCR techniques (see PCR Protocols, A Guide to Methods and Amplifications, Michael et al. Eds, Acad. Press, 1990).

Ligase chain reaction (LCR) is carried out in accordance with known techniques (Weiss, 1991, Science 254:1292). Adaptation of the protocol to meet the desired needs can be carried out by a person of ordinary skill. Strand displacement amplification (SDA) is also carried out in accordance with known techniques or adaptations thereof to meet the particular needs (Walker et al., 1992, Proc. Natl. Acad. Sci. USA 89:392-396; and *ibid.*, 1992, Nucleic Acids Res. 20:1691-1696).

As used herein, the term "gene" is well known in the art and relates to a nucleic acid sequence defining a single protein or polypeptide. A "structural gene" defines a DNA sequence which is transcribed into RNA and translated into a protein having a specific amino acid sequence thereby giving rise to a specific polypeptide or protein. It will be readily recognized by the person of ordinary skill, that the nucleic

acid sequence of the present invention can be incorporated into anyone of numerous established kit formats which are well known in the art.

5 A "heterologous" (i.e. a heterologous gene) region of a DNA molecule is a subsegment of DNA within a larger segment that is not found in association therewith in nature. The term "heterologous" can be similarly used to define two polypeptidic segments not joined together in nature. Non-limiting examples of heterologous genes include reporter genes such as luciferase, chloramphenicol acetyl transferase, beta-galactosidase, and the like which can be juxtaposed or joined to
10 heterologous control regions or to heterologous polypeptides.

The term "vector" is commonly known in the art and defines a plasmid DNA, phage DNA, viral DNA and the like, which can serve as a DNA vehicle into which DNA of the present invention can be cloned. Numerous types of vectors exist and are well known in the art.

15 The term "expression" defines the process by which a gene is transcribed into mRNA (transcription), the mRNA is then being translated (translation) into one polypeptide (or protein) or more.

The terminology "expression vector" defines a vector or vehicle as described above but designed to enable the expression of an
20 inserted sequence following transformation into a host. The cloned gene (inserted sequence) is usually placed under the control of control element sequences such as promoter sequences. The placing of a cloned gene under such control sequences is often referred to as being operably linked to control elements or sequences.

25 Operably linked sequences may also include two segments that are transcribed onto the same RNA transcript. Thus, two sequences, such as a promoter and a "reporter sequence" are operably linked if transcription commencing in the promoter will produce an RNA transcript of the reporter sequence. In order to be "operably linked" it is

not necessary that two sequences be immediately adjacent to one another.

Expression control sequences will vary depending on whether the vector is designed to express the operably linked gene in a prokaryotic or eukaryotic host or both (shuttle vectors) and can additionally contain transcriptional elements such as enhancer elements, termination sequences, tissue-specificity elements, and/or translational initiation and termination sites.

Prokaryotic expressions are useful for the preparation of large quantities of the protein encoded by the DNA sequence of interest. This protein can be purified according to standard protocols that take advantage of the intrinsic properties thereof, such as size and charge (i.e. SDS gel electrophoresis, gel filtration, centrifugation, ion exchange chromatography...). In addition, the protein of interest can be purified via affinity chromatography using polyclonal or monoclonal antibodies. The purified protein can be used for therapeutic applications.

The DNA construct can be a vector comprising a promoter that is operably linked to an oligonucleotide sequence of the present invention, which is in turn, operably linked to a heterologous gene, such as the gene for the luciferase reporter molecule. "Promoter" refers to a DNA regulatory region capable of binding directly or indirectly to RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. For purposes of the present invention, the promoter is bound at its 3' terminus by the transcription initiation site and extends upstream (5' direction) to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. Within the promoter will be found a transcription initiation site (conveniently defined by mapping with S1 nuclease), as well as protein binding domains (consensus sequences) responsible for the

binding of RNA polymerase. Eukaryotic promoters will often, but not always, contain "TATA" boxes and "GCAT" boxes. Prokaryotic promoters contain Shine-Dalgarno sequences in addition to the -10 and -35 consensus sequences.

5 In accordance with one embodiment of the present invention, an expression vector can be constructed to assess the functionality of specific alleles of the SCN1A, SCN2A and SCN3A sodium channels. Non-limiting examples of such expression vectors include a vector comprising the nucleic acid sequence encoding one of the sodium
10 channels (or part thereof) according to the present invention. These vectors can be transfected in cells. The sequences of the alpha subunit of the sodium channels in accordance with the present invention and their structure-function relationship could be assessed by a number of methods known to the skilled artisan. One non-limiting example includes the use of
15 cells expressing the β -1 and β -2 subunits and the sequence of an alpha subunit in accordance with the present invention. For example, an alpha subunit having a mutation, which is linked to epilepsy, could be compared to a sequence devoid of that mutation, as a control. In such cells, the functionality of the sodium channel could be tested as known to the skilled
20 artisan and these cells could be used to screen for agents which could modulate the activity of the sodium channel. For example, agents could be tested and selected, which would reduce the hyperexcitability state of the sodium channel (e.g. their reduction in fast inactivation). Agents known to the person of ordinary skill as affecting other sodium channels
25 could be tested, for example, separately or in batches. Of course, it will be understood that the SCN1A, SCN2A and/or SCN3A genes expressed by these cells can be modified at will (e.g. by *in vitro* mutagenesis or the like).

As used herein, the designation "functional derivative" denotes, in the context of a functional derivative of a sequence whether a

nucleic acid or amino acid sequence, a molecule that retains a biological activity (either function or structural; e.g. sodium channel function or structure) that is substantially similar to that of the original sequence. This functional derivative or equivalent may be a natural derivative or may be prepared synthetically. Such derivatives include amino acid sequences having substitutions, deletions, or additions of one or more amino acids, provided that the biological activity of the protein is conserved. The same applies to derivatives of nucleic acid sequences which can have substitutions, deletions, or additions of one or more nucleotides, provided that the biological activity of the sequence is generally maintained. When relating to a protein sequence, the substituting amino acid generally has chemico-physical properties which are similar to that of the substituted amino acid. The similar chemico-physical properties include, similarities in charge, bulkiness, hydrophobicity, hydrophylicity and the like. The term "functional derivatives" is intended to include "fragments", "segments", "variants", "analogs" or "chemical derivatives" of the subject matter of the present invention. The genetic code, the chemico-physical characteristics of amino acids and teachings relating to conservative vs. non-conservative mutations are well-known in the art. Non-limiting examples of textbooks teaching such information are Stryer, Biochemistry, 3rd ed.; and Lehninger, Biochemistry, 3rd ed. The functional derivatives of the present invention can be synthesized chemically or produced through recombinant DNA technology. all these methods are well known in the art.

The term "variant" refers herein to a protein or nucleic acid molecule which is substantially similar in structure and biological activity to the protein or nucleic acid of the present invention.

As used herein, "chemical derivatives" is meant to cover additional chemical moieties not normally part of the subject matter of the invention. Such moieties could affect the physico-chemical

characteristic of the derivative (i.e. solubility, absorption, half life, decrease of toxicity and the like). Such moieties are exemplified in Remington's Pharmaceutical Sciences (1980). Methods of coupling these chemical-physical moieties to a polypeptide or nucleic acid sequence are well known in the art.

The term "allele" defines an alternative form of a gene which occupies a given locus on a chromosome.

As commonly known, a "mutation" is a detectable change in the genetic material which can be transmitted to a daughter cell. As well known, a mutation can be, for example, a detectable change in one or more deoxyribonucleotide. For example, nucleotides can be added, deleted, substituted for, inverted, or transposed to a new position. Spontaneous mutations and experimentally induced mutations exist. The result of a mutations of nucleic acid molecule is a mutant nucleic acid molecule. A mutant polypeptide can be encoded from this mutant nucleic acid molecule.

As used herein, the term "purified" refers to a molecule having been separated from a cellular component. Thus, for example, a "purified protein" has been purified to a level not found in nature. A "substantially pure" molecule is a molecule that is lacking in all other cellular components.

As used herein, "SCNA biological activity" refers to any detectable biological activity of SCN1A, SCN2A or SCN3A gene or protein (herein sometimes collectively called SCNA genes or SCNA proteins). This includes any physiological function attributable to an SCNA gene or protein. It can include the specific biological activity of SCNA proteins which is efflux of sodium or related ions. This includes measurement of channel properties such as, but not limited to: 1) the voltage-dependence of activation, a measure of the strength of membrane depolarization

necessary to open the channels, 2) the voltage-dependence of steady state inactivation, a measure of the fraction of channels available to open at the resting membrane potential; and 3) the time course of inactivation. At a larger scale, SCNA biological activity includes transmission of impulses through cells, wherein changes in transmission characteristics caused by modulators of SCNA proteins can be identified. Non-limiting examples of such measurements of these biological activities may be made directly or indirectly, such as through the transient accumulation of ions in a cell, dynamics of membrane depolarization, etc. SCNA biological activity is not limited, however, to these most important biological activities herein identified. Biological activities may also include simple binding or pKa analysis of SCNA with compounds, substrates, interacting proteins, and the like. For example, by measuring the effect of a test compound on its ability to increase or inhibit such SCNA binding or interaction is measuring a biological activity of SCNA according to this invention. SCNA biological activity includes any standard biochemical measurement of SCNA such as conformational changes, phosphorylation status or any other feature of the protein that can be measured with techniques known in the art. Finally, SCNA biological activity also includes activities related to SCNA gene transcription or translation, or any biological activities of such transcripts or translation products.

As used herein, the terms "molecule", "compound", "agent" or "ligand" are used interchangeably and broadly to refer to natural, synthetic or semi-synthetic molecules or compounds. The term "molecule" therefore denotes for example chemicals, macromolecules, cell or tissue extracts (from plants or animals) and the like. Non limiting examples of molecules include nucleic acid molecules, peptides, ligands (including, for example, antibodies and carbohydrates) and pharmaceutical agents. The agents can be selected and screened by a

variety of means including random screening, rational selection and by rational design using for example protein or ligand modelling methods such as computer modelling. The terms "rationally selected" or "rationally designed" are meant to define compounds which have been chosen
5 based on the configuration of the interacting domains of the present invention. As will be understood by the person of ordinary skill, macromolecules having non-naturally occurring modifications are also within the scope of the term "molecule". For example, peptidomimetics, well known in the pharmaceutical industry and generally referred to as
10 peptide analogs can be generated by modelling as mentioned above. Similarly, in a preferred embodiment, the polypeptides of the present invention are modified to enhance their stability. It should be understood that in most cases this modification should not alter the biological activity of the protein. The molecules identified in accordance with the teachings
15 of the present invention have a therapeutic value in diseases or conditions in which sodium transport through the sodium channels is compromised by a mutation (or combination thereof) in one of the genes identified in accordance with the present invention. Alternatively, the molecules identified in accordance with the teachings of the present invention find
20 utility in the development of compounds which can modulate the activity of the alpha subunit sodium channels and/or the action potential in nerve cells and muscles cells (e.g. restore the fast inactivation of the sodium channel to normal levels).

As used herein, agonists and antagonists also include
25 potentiators of known compounds with such agonist or antagonist properties. In one embodiment, modulators of the fast inactivation of the sodium channel in accordance with the present invention can be identified and selected by contacting the indicator cell with a compound or mixture or library of molecules for a fixed period of time.

As used herein the recitation "indicator cells" refers to cells that express at least one sodium channel α subunit (SCNA) according to the present invention. As alluded to above, such indicator cells can be used in the screening assays of the present invention. In certain embodiments, the indicator cells have been engineered so as to express a chosen derivative, fragment, homolog, or mutant of the combination of genotypes of the present invention. The cells can be yeast cells or higher eukaryotic cells such as mammalian cells. In one particular embodiment, the indicator cell would be a yeast cell harboring vectors enabling the use of the two hybrid system technology, as well known in the art (Ausubel et al., 1994, *supra*) and can be used to test a compound or a library thereof. In another embodiment, the *cis-trans* assay as described in USP 4,981,784, can be adapted and used in accordance with the present invention. Such an indicator cell could be used to rapidly screen at high-throughput a vast array of test molecules. In a particular embodiment, the reporter gene is luciferase or beta-Gal.

It shall be understood that the "*in vivo*" experimental model can also be used to carry out an "*in vitro*" assay. For example, cellular extracts from the indicator cells can be prepared and used in an "*in vitro*" test. A non-limiting example thereof include binding assays.

In some embodiments, it might be beneficial to express a fusion protein. The design of constructs therefor and the expression and production of fusion proteins and are well known in the art (Sambrook et al., 1989, *supra*; and Ausubel et al., 1994, *supra*).

Non-limiting examples of such fusion proteins include hemagglutinin fusions and Gluthione-S-transferase (GST) fusions and Maltose binding protein (MBP) fusions. In certain embodiments, it might be beneficial to introduce a protease cleavage site between the two polypeptide sequences which have been fused. Such protease cleavage

sites between two heterologously fused polypeptides are well known in the art.

In certain embodiments, it might also be beneficial to fuse the protein of the present invention to signal peptide sequences enabling a secretion of the fusion protein from the host cell. Signal peptides from diverse organisms are well known in the art. Bacterial OmpA and yeast Suc2 are two non-limiting examples of proteins containing signal sequences. In certain embodiments, it might also be beneficial to introduce a linker (commonly known) between the interaction domain and the heterologous polypeptide portion. Such fusion protein find utility in the assays of the present invention as well as for purification purposes, detection purposes and the like.

For certainty, the sequences and polypeptides useful to practice the invention include without being limited thereto mutants, homologs, subtypes, alleles and the like. It shall be understood that generally, the sequences of the present invention should encode a functional (albeit defective) alpha subunit of sodium channels (SCNA). It will be clear to the person of ordinary skill that whether the SCNA sequence of the present invention, variant, derivative, or fragment thereof retains its function, can be determined by using the teachings and assays of the present invention and the general teachings of the art.

It should be understood that the SCNA protein of the present invention can be modified, for example by *in vitro* mutagenesis, to dissect the structure-function relationship thereof and permit a better design and identification of modulating compounds. However, some derivative or analogs having lost their biological function may still find utility, for example for raising antibodies. These antibodies could be used for detection or purification purposes. In addition, these antibodies could

also act as competitive or non-competitive inhibitor and be found to be modulators of the activity of the SCNA proteins of the present invention.

A host cell or indicator cell has been "transfected" by exogenous or heterologous DNA (e.g. a DNA construct) when such DNA has been introduced inside the cell. The transfecting DNA may or may not be integrated (covalently linked) into chromosomal DNA making up the genome of the cell. In prokaryotes, yeast, and mammalian cells for example, the transfecting DNA may be maintained on an episomal element such as a plasmid. With respect to eukaryotic cells, a stably transfected cell is one in which the transfecting DNA has become integrated into a chromosome so that it is inherited by daughter cells through chromosome replication. This stability is demonstrated by the ability of the eukaryotic cell to establish cell lines or clones comprised of a population of daughter cells containing the transfecting DNA. Transfection methods are well known in the art (Sambrook et al., 1989, *supra*; Ausubel et al., 1994 *supra*). The use of a mammalian cell as indicator can provide the advantage of furnishing an intermediate factor, which permits for example the interaction of two polypeptides which are tested, that might not be present in lower eukaryotes or prokaryotes. It will be understood that extracts from mammalian cells for example could be used in certain embodiments, to compensate for the lack of certain factors.

In general, techniques for preparing antibodies (including monoclonal antibodies and hybridomas) and for detecting antigens using antibodies are well known in the art (Campbell, 1984, In "Monoclonal Antibody Technology: Laboratory Techniques in Biochemistry and Molecular Biology", Elsevier Science Publisher, Amsterdam, The Netherlands) and in Harlow et al., 1988 (in: Antibody-A Laboratory Manual, CSH Laboratories). The present invention also provides polyclonal, monoclonal antibodies, or humanized versions

thereof, chimeric antibodies and the like which inhibit or neutralize their respective interaction domains and/or are specific thereto.

From the specification and appended claims, the term therapeutic agent should be taken in a broad sense so as to also include
5 a combination of at least two such therapeutic agents. Further, the DNA segments or proteins according to the present invention could be introduced into individuals in a number of ways. For example, cells can be isolated from the afflicted individual, transformed with a DNA construct according to the invention and reintroduced to the afflicted individual in a
10 number of ways. Alternatively, the DNA construct can be administered directly to the afflicted individual. The DNA construct can also be delivered through a vehicle such as a liposome, which can be designed to be targeted to a specific cell type, and engineered to be administered through different routes.

15 For administration to humans, the prescribing medical professional will ultimately determine the appropriate form and dosage for a given patient, and this can be expected to vary according to the chosen therapeutic regimen (i.e. DNA construct, protein, cells), the response and condition of the patient as well as the severity of the disease.

20 Composition within the scope of the present invention should contain the active agent (i.e. molecule, hormone) in an amount effective to achieve the desired therapeutic effect while avoiding adverse side effects. Typically, the nucleic acids in accordance with the present invention can be administered to mammals (i.e. humans) in doses ranging
25 from 0.005 to 1 mg per kg of body weight per day of the mammal which is treated. Pharmaceutically acceptable preparations and salts of the active agent are within the scope of the present invention and are well known in the art (Remington's Pharmaceutical Science, 16th Ed., Mack Ed.). For the administration of polypeptides, antagonists, agonists and the like, the

amount administered should be chosen so as to avoid adverse side effects. The dosage will be adapted by the clinician in accordance with conventional factors such as the extent of the disease and different parameters from the patient. Typically, 0.001 to 50 mg/kg/day will be administered to the mammal.

The present invention also relates to a kit for diagnosing and/or prognosing epilepsy, and/or predicting response to a medication comprising an assessment of a genotype at SCNA loci of the present invention (or loci in linkage disequilibrium therewith) using a nucleic acid fragment, a protein or a ligand, a restriction enzyme or the like, in accordance with the present invention. For example, a compartmentalized kit in accordance with the present invention includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allow the efficient transfer of reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include in one particular embodiment a container which will accept the test sample (DNA, protein or cells), a container which contains the primers used in the assay, containers which contain enzymes, containers which contain wash reagents, and containers which contain the reagents used to detect the extension products.

BRIEF DESCRIPTION OF THE DRAWINGS

Having thus generally described the invention, reference will now be made to the accompanying drawings, showing by way of illustration a preferred embodiment thereof, and in which:

Figure 1 shows the IGE candidate region on ch 2q23-q31. Order and distance between markers are according to Gyapay et al., 1994.

Figure 2 shows the PCR primers used for genomic
5 PCR-SSCP of SCN1A;

Figure 3 shows the sequence of the SCN1A mutations found in epilepsy patients;

Figure 4 shows the PCR primers used for genomic
10 PCR-SSCP of SCN2A;

Figure 5 shows the mutation found in epilepsy patients in SCN2A;

Figure 6 shows the PCR primers used for genomic PCR-SSCP of SCN3A; and

Figure 7 shows the mutation found in epilepsy patients
15 in SCN3A.

Sequences are also shown in the Sequence Listing. For example, SEQ ID NO.:1 shows the nucleic acid sequence of the adult form of SCN1A; SEQ ID NO.:2 shows the nucleic acid sequence of the neonatal form of SCN1A; SEQ ID NO.:3 shows the protein sequence of the adult form of SCN1A; SEQ ID NO.:4 shows the protein sequence of the neonatal form of SCN1A; SEQ ID NOS.:5-32 show the genomic sequence of SCN1A; SEQ ID NO.:33 shows the cDNA sequence of the adult form of SCN2A; SEQ ID NO.:34 shows the cDNA sequence of the neonatal form of SCN2A; SEQ ID NO.:35 shows the protein sequence of the adult form of SCN2A; SEQ ID NO.:36 shows the protein sequence of the neonatal form of SCN2A; SEQ ID NOS.:37-64 show the genomic sequence of SCN2A; SEQ ID NO.:65 shows the cDNA sequence of the adult form of SCN3A; SEQ ID NO.:66 shows the cDNA sequence of the neonatal form of SCN3A; SEQ ID NO.:67 shows the protein sequence of

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the adult form of SCN3A; SEQ ID NO.:68 shows the protein sequence of the neonatal form of SCN3A; and SEQ ID NOS.:69-98 show the genomic sequence of SCN3A. Rat SCNA1 sequences can be found in GenBank under accession numbers M22253 and X03638.

5 Other objects, advantages and features of the present invention will become more apparent upon reading of the following non-restrictive description of preferred embodiments with reference to the accompanying drawing which is exemplary and should not be interpreted as limiting the scope of the present invention.

10 DESCRIPTION OF THE PREFERRED EMBODIMENT

Epilepsy is one of the most common neurological conditions, affecting 1-2% of the general population. Familial aggregation studies have shown an increased risk for epilepsy in relatives of probands with different types of epilepsy, and especially for the idiopathic
15 generalized epilepsies (IGEs). The epilepsy genes identified to date account for a very small proportion of all the epilepsies. In addition, they have been identified in rare syndromes where the pattern of inheritance was clearly Mendelian. This is not the case for the vast majority of epileptic patients, however, where the pattern of inheritance is not
20 compatible with a simple Mendelian model. In fact, most authors consider epilepsy to be the result of a combination of many different genetic and environmental factors, features of a complex trait. While the pattern of inheritance is not mendelian, sporadic IGE cases may be caused by specific mutations in the same genes. Based on this assumption, a large
25 cohort of IGE patients was tested for mutation in the SCNA genes.

In order to localize the gene causing epilepsy in a large family segregating an autosomal dominant form of IGE, 41 family members, including 21 affected individuals, were genotyped. A detailed clinical description of this family has been reported elsewhere (Scheffer

and Berkovic 1997). The majority of patients in this family present a benign epilepsy syndrome occurring in childhood and characterized by frequent generalized tonic-clonic seizures not always associated with fever: a syndrome called febrile seizures plus (FS+). However, several
5 patients presented other types of generalized seizures (GTCS) as well, such as myoclonic seizures and absences (Scheffer and Berkovic 1997). Mean age at onset was 2.2 years and offset was 11.7 years. Neurological examination and intellect were normal in all individuals except one, who
10 had moderate intellectual disability. EEG recordings were normal in most patients. However, in three individuals generalized epileptiform activity was found and four patients had mild or moderate diffuse background slowing. Table 1 shows the different types of seizures found in the 21 patients included in this study.

Table 1. Different types of generalized seizures found in the 21 patients included in the linkage analysis.

Type of seizures	n
Febrile convulsions alone	9
GTCSs ^a + absence seizures	4
GTCSs + myoclonic seizures	1
GTCSs + atonic seizures	1
Solitary afebrile GTCS	1
Secondary epilepsy + mental retardation	1
Unwitnessed events	4

^a GTCS: generalized tonic clonic seizure

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A genome wide search examining 190 markers identified linkage of IGE to chromosome (ch) 2 based on an initial positive lod score for marker D2S294 ($Z=4.4$, $(=0)$). A total of 24 markers were tested on ch 2q in order to define the smallest IGE candidate region. Table 2 shows the two-point lod scores for 17 markers spanning the IGE candidate region. The highest lod score ($Z_{max}=5.29$; $(=0)$) was obtained with marker D2S324. Critical recombination events mapped the IGE gene to a 29cM region flanked by markers D2S156 and D2S311, assigning the IGE locus to ch 2q23-q31 (Figure 1). Although the relationship of FS+ with other IGE phenotypes remains unclear, the observation that in this family, several affected individuals have different types of generalized seizures, suggests that seizure predisposition determined by the ch 2q-IGE gene could be modified by other genes and/or environmental factors, to produce different seizure types.

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Table 2. Two-point lod-scores for 17 markers localized
on ch 2q23-q31.

Locus	Recombination fractions							Zmax	max
	0	0.05	0.1	0.15	0.2	0.3	0.4		
D2S142	0.99	1.94	1.97	1.85	1.68	1.22	0.66	1.98	0.078
D2S284	1.3	1.18	1.06	0.94	0.82	0.57	0.3	1.3	0
D2S306	1.9	2.82	2.74	2.52	2.25	1.6	0.85	2.82	0.057
D2S156	2.15	3.05	2.96	2.73	2.43	1.73	0.93	3.05	0.056
D2S354	4.72	4.26	3.82	3.4	2.97	2.1	1.13	4.72	0
D2S111	5.15	4.71	4.26	3.78	3.29	2.26	1.17	5.15	0
D2S124	3.5	3.2	2.89	2.58	2.26	1.58	0.84	3.5	0
D2S382	4.31	3.93	3.54	3.14	2.74	1.91	1.02	4.31	0
D2S399	0.48	0.4	0.33	0.27	0.22	0.14	0.08	0.48	0
D2S294	4.4	4.04	3.65	3.25	2.84	2	1.07	4.4	0
D2S335	4.76	4.32	3.91	3.51	3.1	2.22	1.21	4.76	0
D2S333	1.42	1.23	1.04	0.87	0.72	0.45	0.22	1.4	0
D2S324	5.29	4.72	4.16	3.63	3.13	2.15	1.14	5.29	0
D2S384	3.85	3.52	3.17	2.82	2.45	1.69	0.89	3.85	0
D2S152	1.9	1.7	1.52	1.36	1.2	0.87	0.48	1.9	0
D2S311	-0.81	1.62	1.66	1.58	1.46	1.11	0.63	1.66	0.085
D2S155	-5.21	0.57	1.12	1.29	1.29	1.04	0.59	1.3	0.17

Haplotypes using 17 markers spanning the IGE candidate region were constructed (data not shown). The centromeric boundary was defined by a recombination event between the markers D2S156 and D2S354; whereas a recombination between the markers D2S152 and D2S311 set the telomeric boundary. These critical recombination events localized the IGE gene to a 29cM region flanked by markers D2S156 and D2S311 (Figure 1).

Over the last four decades, family studies provided two important pieces of evidence supporting the role of genetic factors in determining susceptibility to seizures: 1) familial aggregation studies have shown evidence for an increased risk for epilepsy in relatives of probands with different types of epilepsy. In two studies standardized morbidity ratios for unprovoked seizures in relatives of individuals with idiopathic childhood-onset epilepsy varied from 2.5 to 3.4 in siblings and 6.7 in offspring (Anneger et al. 1982; Ottman et al. 1989); and 2) the presence of higher concordance rates for epilepsy in monozygotic than in dizygotic twins. Different studies showed concordance rates varying from 54 to 11 % in monozygotic twins and 10 to 5% in dizygotic pairs (Inouye 1960; Lennox, 1960; Harvald and Hauge 1965; Corey et al. 1991; Silanpaa et al 1991).

It is now generally accepted that seizure susceptibility probably reflects complex interactions of multiple factors affecting neuronal excitability and that most common genetic epilepsies display familial aggregation patterns that are not explained by segregation of a single autosomal gene (Andermann 1982; Ottman et al. 1995). This of course significantly makes more complex one's ability to isolate genes which predispose or induce epilepsy. However, some specific epileptic syndromes, which aggregate in families, may result from definable monogenic abnormalities. These families present a unique opportunity to

rapidly map genes that play a role in determining predisposition to seizures.

To date, there are a total of six loci (Greenberg et al. 1988; Leppert et al 1989; Lewis et al. 1993; Elmslie et al. 1997; Guipponi et al. 1997; Wallace et al. 1998), for which three genes have been identified in specific IGE syndromes (Bievert et al. 1998; Singh et al. 1998; Wallace et al. 1998). Interestingly, all three genes are ion channels, including a mutation found in the Na⁺-channel (1 in a Tasmania family with febrile seizures and generalized epilepsy (Wallace et al. 1998). While the candidate interval identified in our kindred remains large, a number of interesting genes map to the region. These include a cluster of Na⁺ channel genes and K⁺ channel genes (electronic data base search), as well as the GAD1 gene, which encodes for glutamate decarboxylase, an enzyme involved in the syntheses of γ -aminobutyric acid (GABA) (Bu and Tobin 1994). GABA is one of the major neurotransmitters involved in synaptic inhibition in the central nervous system (Barnard et al. 1987). However, the large size of the candidate interval will require further refinement of the locus prior to the identification of the gene responsible for IGE in the kindred studied herein.

Fifty-three % (9/17) of affected individuals in the large IGE family described herein, who had their seizures classified, had only febrile convulsions. However, 41 % of patients (7/17) presented with different types of generalized seizures. These findings may indicate that, although the predisposition to IGE in this family is determined by a single gene localized on ch2q23-q31, the different types of generalized seizures occurring in the same family may have resulted from interactions among genetic and/or environmental modifiers.

In conclusion, a locus for IGE was mapped on ch 2q23-q31. This locus seems to be associated with a specific IGE syndrome, FS

+. However, the relationship of FS+ with other IGE phenotypes, and the role of the ch 2q locus in other FS+ families and in other forms of IGE are still undetermined.

Having identified a locus for IGE on chromosome 2q23-q31, it was next verified whether mutations and/or polymorphisms could be linked to epilepsy. Public data bases were screened to identify potential genes in that chromosome region. The blasts of the data bases were also oriented to identify more specifically, membrane channels since seizures in mice and human are known to be associated with membrane channels. Having identified membrane channel coding sequences or parts thereof by the computer searches, the candidate genes, potentially involved in epilepsy, had to be validated as susceptibility genes for the disease. Two approaches were used. The first one was to test the candidate genes for mutations in a family comprising members having the disease (data not shown). The second approach was as follows. Since it is known that epilepsy results from a lower seizure threshold, and that generalized epilepsy results, in many instances, from a generalized lowering of the seizure threshold, the following hypothesis was formulated. The gene which results in epilepsy in the large family (that enabled the focusing chromosome 2q23-q31) should have other, less severe, mutations that would cause epilepsy in people who have only a weak family history of epilepsy. The sodium channel genes were chosen because they are involved in key electrical functions and could thus be good candidates. To formally test the hypothesis, many (60 to 70) unrelated cases of epilepsy were tested for mutations in these candidate genes. Surprisingly, mutations were found in all three candidate genes.

In order to assess whether mutations/polymorphisms could be identified and correlated to epilepsy, a panel of 70 to 80 epileptic patients (IGE) were tested for mutations in SCN1A, SCN2A and SCN3A,

using Single-strand conformation polymorphism (SSCP). SSCP analysis enables the detection of mutations as small as single-base substitutions. Indeed, such substitutions, by altering the conformations of single-strand DNA molecules, affect the electrophoretic mobilities thereof in non-denaturing gels. Thus, one can distinguish among sequences by comparing the mobilities of wild type (wt), mutant DNA, or different alleles of a given locus. The identification of single base substitutions of genes using SSCP is well known in the art, and numerous protocols are available therefor. A non-limiting example thereof includes fluorescence-based SSCP analysis, following PCR carried out using fluorescent-labeled primers specific for the DNA regions one wishes to amplify.

Upon the identification of differences between normal and epileptic mobilities for one of the SCNA loci of the present invention, the amplified fragments were sequenced and the nucleic acid sequences between a normal patient and an epileptic patient (IGE) compared. This comparison enabled the identification of mutations in SCN1A, SCN2A, and SCN3A. To assess, whether this difference in sequence or mutation was significantly associated with the disease, SSCP analysis was performed once again using a large cohort of normal patients. This analysis enabled to show that the mutations identified by SSCP and confirmed by sequence analysis were not present in the large cohort of normal patients tested, thereby showing that the mutations identified correlated with IGE, for the population tested.

Taken together, these results show that SCN1A, SCN2A and SCN3A are validated genes associated with epilepsy and more specifically with IGE.

This invention now establishes, for the first time, that SCN1A, SCN2A, and SCN3A, is directly responsible for idiopathic generalized epilepsy (IGE) in certain human populations. Further, this

discovery suggests that compounds which modulate the activity of SCN1A, SCN2A and SCN3A may have application far beyond the small groups of families with IGE, and may have applicability for treating many or all forms of epilepsy and related neurological disorders. It is therefore
5 an object of this invention to provide screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders. This invention also claims those compounds, the use of these compounds in treating epilepsy and related neurological disorders, and any use of any
10 compounds identified using such a screening assay in treating epilepsy and related neurological disorders.

Generally, high throughput screens for one or more SCN1A, SCN2A or SCN3A (herein collectively called SCNA) sodium channels modulators i.e. candidate or test compounds or agents (e.g.,
15 peptides, peptidomimetics, small molecules or other drugs) may be based on assays which measure biological activity of SCNA. The invention therefore provides a method (also referred to herein as a "screening assay") for identifying modulators, which have a stimulatory or inhibitory effect on, for example, SCNA biological activity or expression, or which
20 bind to or interact with SCNA proteins, or which have a stimulatory or inhibitory effect on, for example, the expression or activity of SCNA interacting proteins (targets) or substrates.

Examples of methods available for cell-based assays and instrumentation for screening ion-channel targets are described in the
25 review by Gonzalez et al. (Drug Discov. Today 4:431-439, 1999), and high-throughput screens for ion-channel drugs are described in review by Denyer et al. (Drug Discov. Today 3:323-332, 1998). Such assays include efflux of sodium or related ions that can be measured in a cell line (recombinant or non-recombinant) using fluorescence-based assays using

both sodium indicator dyes and voltage sensing dyes. Preferred assays employ ^{14}C guanidine flux and/or sodium indicator dyes such as SBFI and voltage sensing dyes such as DiBAC. Oxonal dyes such as DiBAC₄ are responsive to membrane depolarization. Hyper-polarization results in
5 removal of the dye from the cell by passive diffusion, while depolarization results in concentration of the dye within the cell.

In one embodiment, the invention provides assays for screening candidate or test compounds which interact with substrates of a SCNA protein or biologically active portion thereof.

10 In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a SCNA protein or polypeptide or biologically active portion thereof.

In one embodiment, an assay is a cell-based assay in
15 which a cell which expresses a SCNA protein or biologically active portion thereof, either natural or recombinant in origin, is contacted with a test compound and the ability of the test compound to modulate SCNA biological activity, e.g., modulation of sodium efflux activity, or binding to a sodium channel or a portion thereof, or any other measurable biological
20 activity of SCNA is determined. Determining the ability of the test compound to modulate SCNA activity can be accomplished by monitoring, for example, the release of a neurotransmitter or other compound, from a cell which expresses SCNA such as a neuronal cell, e.g. a substantia nigra neuronal cell, or a cardiac cell upon exposure of the test compound
25 to the cell. Furthermore, determining the ability of the test compound to modulate SCNA activity can be accomplished by monitoring, for example, the change in current or the change in release of a neurotransmitter from a cell which expresses SCNA upon exposure to a test compound. Currents in cells can be measured using the patch-clamp technique as

described in the Examples below using the techniques described in, for example, Hamill et al. 1981 Pfluegers Arch. 391:85-100. Alternatively, changes in current can be measured by dye based fluorescence assays described below.

- 5 Determining the ability of the test compound to modulate binding of SCNA to a substrate can be accomplished, for example, by coupling the SCNA agent or substrate with a radioisotope or enzymatic label such that binding of the SCNA substrate to SCNA can be determined by detecting the labeled SCNA substrate in a complex. For
10 example, compounds (e.g., SCNA agents or substrates) can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting radio-emission or by scintillation counting. Alternatively, compounds can be enzymatically labeled with, for example, horseradish peroxidase or alkaline phosphatase. In these assays,
15 compounds which inhibit or increase substrate binding to SCNA are useful for the therapeutic objectives of the invention.

 It is also within the scope of this invention to determine the ability of a compound (e.g. SCNA substrate) to interact with SCNA without the labeling of any of the interactants. For example, a
20 microphysiometer can be used to detect the interaction of a compound with SCNA without the labeling of either the compound or the SCNA (McConnell H.M. et al. (1992), Science 257:1906-1912). As used herein, a "microphysiometer" (e.g., Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-
25 addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and SCNA.

 Modulators of SCNA can also be identified through the changes they induce in membrane potential. A suitable instrument for

measuring such changes is the VIPR™ (voltage ion probe reader) from Aurora Biosciences. This instrument works together with a series of voltage-sensing ion probe assays. The probes sense changes in transmembrane electrical potential through a voltage-sensitive FRET
5 mechanism for which the ratio donor fluorescence emission to acceptor fluorescence emission reveals the extent of cell depolarization for both sodium and potassium channels. Depolarization results from transport of a quencher across the membrane and far enough away from a membrane-bound fluorescence emitter to relieve the initial quenching and
10 produce light at the emission wavelength of the emitter. The system follows fluorescence at two wavelengths, both the intensities and ratios change during cell depolarization. The reader permits detection of sub-second, real-time optical signals from living cells in a microplate format. The system is amenable to manual operation for assay development or
15 automation via robots for high-throughput screening.

In another embodiment, the assay is a cell-based assay comprising a contacting of a cell containing a target molecule (e.g. another molecule, substrate or protein that interacts with or binds to SCNA) with a test compound and determining the ability of the test
20 compound to indirectly modulate (e.g. stimulate or inhibit) the biological activity of SCNA by binding or interacting with the target molecule. Determining the ability of the test compound to indirectly modulate the activity of SCNA can be accomplished, for example, by determining the ability of the test compound to bind to or interact with the target molecule
25 and thereby to indirectly modulate SCNA, to modulate sodium efflux, or to modulate other biological activities of SCNA. Determining the ability of the SCNA protein or a biologically active fragment thereof, to bind to or interact with the target molecule can be accomplished by one of the methods described above or known in the art for determining direct

binding. In a preferred embodiment, determining the ability of the test compound's ability to bind to or interact with the target molecule and thereby to modulate the SCNA protein can be accomplished by determining a secondary activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (e.g. intracellular Ca^{2+} , diacylglycerol, IP3, and the like), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (comprising a target -responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, such as luciferase), or detecting a target-regulated cellular response such as the release of a neurotransmitter. Alternatively, recombinant cell lines may employ recombinant reporter proteins which respond, either directly or indirectly to sodium efflux or secondary messengers all as known in the art.

In yet another embodiment, an assay of the present invention is a cell-free assay in which a SCNA protein or biologically active portion thereof, either naturally occurring or recombinant in origin, is contacted with a test compound and the ability of the test compound to bind to, or otherwise modulate the biological activity of, the SCNA protein or biologically active portion thereof is determined. Preferred biologically active portions of the SCNA proteins to be used in assays of the present invention include fragments which participate in interactions with non-SCNA molecules, (e.g. other channels for sodium, potassium or Ca^{+} or fragments thereof, or fragments with high surface probability scores for protein-protein or protein-substrate interactions). Binding of the test compound to the SCNA protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the SCNA protein or biologically active portion thereof

with a known compound which binds SCNA to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a SCNA protein, wherein determining the ability of the test compound to interact with a SCNA
5 protein comprises determining the ability of the test compound to preferentially bind to SCNA or biologically active portion thereof as compared to the known compound.

In another embodiment, the assay is a cell-free assay in which a SCNA protein or biologically active portion thereof is contacted
10 with a test compound and the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the SCNA protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate the activity of a SCNA protein can be accomplished, for example, by determining the ability of the SCNA protein
15 to bind to a SCNA target molecule by one of the methods described above for determining direct binding. Determining the ability of the SCNA protein to bind to a SCNA target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA, Sjolander, S. and Urbaniczky, C. (1991) Anal. Chem. 63:2338-2345
20 and Szabo et al. (1995) Curr. Opin. Struct. Biol. 5:699- 705). As used herein, "BIA" refers to a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g. BIA core). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological
25 molecules.

In an alternative embodiment, determining the ability of the test compound to modulate the activity of a SCNA protein can be accomplished by determining the ability of the test compound to modulate the activity of an upstream or downstream effector of a SCNA target

molecule. For example, the activity of the test compound on the effector molecule can be determined or the binding of the effector to SCNA can be determined as previously described.

The cell-free assays of the present invention are
5 amenable to use of both soluble and/or membrane-bound forms of isolated proteins. In the case of cell-free assays in which a membrane-bound form of an isolated protein is used (e.g. a sodium channel) it may be desirable to utilize a solubilizing agent such that the membrane-bound form of the isolated protein is maintained in solution. Examples of such
10 solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton® X-100, Triton® X-114, Thesit®, Isotridecypoly(ethylene glycol ether)n, 3-[(3-cholamidopropyl)dimethylamino]-1-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl)dimethylamino]-2-hydroxy-1-propane sulfonate (CHAPSO), or N-dodecyl-N,N-dimethyl-3-ammnonio-1-propane sulfonate.
15

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either SCNA or its target molecule to facilitate separation of complexed from
20 uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a SCNA protein or interaction of a SCNA protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants.
25 Examples of such vessels include microtitre plates, test tubes and micro-centrifuge tubes. In one embodiment a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/SCNA fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto

glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or SCNA protein and the mixture incubated under conditions conducive to complex formation (e.g. at physiological conditions for salt and pH). Following incubation the beads or microtitre plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of SCNA binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices (and well-known in the art) can also be used in the screening assays of the invention. For example, either a SCNA protein or a SCNA target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated SCNA protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with SCNA protein or target molecules but which do not interfere with binding of the SCNA protein to its target molecule can be derivatized to the wells of the plate, and unbound target or SCNA protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST -immobilized complexes, include immunodetection of complexes using antibodies reactive with the SCNA protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the SCNA protein or target molecule.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate vesicular traffic and protein transport in a cell, e.g. a neuronal or cardiac cell using the assays described in for example Komada M. et al. (1999) Genes Dev.13(11):1475-85, and Roth M.G. et al. (1999) Chem. Phys. Lipids. 98(12):141-52.

In another preferred embodiment candidate, or test compounds or agents are tested for their ability to inhibit or stimulate or regulate the phosphorylation state of a SCNA channel protein or portion thereof, or an upstream or downstream target protein, using for example an *in vitro* kinase assay. Briefly, a SCNA target molecule (e.g. an immunoprecipitated sodium channel from a cell line expressing such a molecule), can be incubated with radioactive ATP, e.g., [γ - 32 P] - ATP, in a buffer containing MgCl₂ and MnCl₂, e.g., 10 mM MgCl₂ and 5 mM MnCl₂. Following the incubation, the immunoprecipitated SCNA target molecule (e.g. the sodium channel), can be separated by SDS-polyacrylamide gel electrophoresis under reducing conditions, transferred to a membrane, e.g., a PVDF membrane, and autoradiographed. The appearance of detectable bands on the auto radiograph indicates that the SCNA substrate, e.g., the sodium channel, has been phosphorylated. Phosphoaminoacid analysis of the phosphorylated substrate can also be performed in order to determine which residues on the SCNA substrate are phosphorylated. Briefly, the radiophosphorylated protein band can be excised from the SDS gel and subjected to partial acid hydrolysis. The products can then be separated by one-dimensional electrophoresis and analyzed on, for example, a phosphoimager and compared to ninhydrin-stained phosphoaminoacid standards. Assays such as those described in, for example, Tamaskovic R. et al. (1999) Biol. Chem. 380(5):569-78.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to associate with (e.g. bind) calcium, using for example, the assays described in Liu L. (1999) Cell Signal. 11(5):317-24 and Kawai T. et al. (1999) Oncogene 18(23):3471-80.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate chromatin formation in a cell using for example the assays described in Okuwaki M. et al. (1998) J. Biol. Chem. 273(51):34511-8 and Miyaji- Yamaguchi M. (1999) J. Mol. Biol. 290(2): 547-557.

In yet another preferred embodiment candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate cellular proliferation, using for example, the assays described in Baker F.L. et al. (1995) Cell Prolif. 28(1):1-15, Cheviron N. et al. (1996) Cell Prolif. 29(8):437-46. Hu Z. W. et al. (1999) J: Pharmacol. Exp. Ther. 290(1):28-37 and Elliott K. et al. (1999) Oncogene 18(24):3564-73.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to regulate its association with the cellular cytoskeleton. Using for example, the assays similar to those described in Gonzalez C. et al. (1998) Cell Mol. Biol. 44(7):1117-27 and Chia C.P. et al. (1998) Exp. Cell Res. 244(1):340-8.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate membrane excitability, using for example, the assays described in Bar-Sagi D. et al. (1985) J. Biol. Chem. 260(8):4740-4 and Barker J.L. et al. (1984) Neurosci. Lett. 47(3):313-8.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate cytokine signaling in a cell, (e.g., a neuronal or cardiac cell), the assays described in Nakashima Y. et al. (1999)J: Bone Joint Surg. Am. 81 (5):603-15.

5 In another embodiment, modulators of SCNA expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of SCNA mRNA or protein in the cell is determined. The level of expression of SCNA mRNA or protein in the presence of the candidate compound is compared to the level of expression of SCNA mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of SCNA expression based on this comparison. For example, when expression of SCNA mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of SCNA mRNA or protein expression. Alternatively, when expression of SCNA mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of SCNA mRNA or protein expression. The level of SCNA mRNA or protein expression in the cells can be determined by methods described herein or other methods known in the art for detecting SCNA mRNA or protein.

25 The assays described above may be used as initial or primary screens to detect promising lead compounds for further development. Often, lead compounds will be further assessed in additional, different screens. Therefore, this invention also includes secondary SCNA screens which may involve electrophysiological assays utilizing mammalian cell lines expressing the SCNA channels such as

patch clamp technology or two electrode voltage clamp and FRET-based voltage sensor. Standard patch clamp assays express wild type and mutant channels in *Xenopus* oocytes, and examine their properties using voltage-clamp electrophysiological recording. Wild type sodium channels
5 are closed at hyperpolarized membrane potentials. In response to membrane depolarization the channels open within a few hundred microseconds, resulting in an inward sodium flux, which is terminated within a few milliseconds by channel inactivation. In whole cell recordings, rapid activation and inactivation of thousands of sodium channels
10 distributed throughout the cell membrane results in a transient inward sodium current that rises rapidly to peak amplitude and then decays to baseline within a few milliseconds.

Tertiary screens may involve the study of the identified modulators in rat and mouse models for epilepsy. Accordingly, it is within
15 the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, a test compound identified as described herein (e.g., a SCNA modulating agent, an antisense SCNA nucleic acid molecule, a SCNA-specific antibody, or a SCNA-binding partner) can be used in an animal model to determine the
20 efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatment (e.g. treatments of
25 different types of epilepsy or CNS disorders), as described herein.

The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic

library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, Anticancer Drug Des. 12: 145, 1997). Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) Proc. Natl. Acad. Sci. USA. 90:6909; Erb et al. (1994) Proc. Natl. Acad. Sci. USA 91:11422; Zuckermann et al. (1994), J. Med. Chem. 37:2678; Cho et al. (1993) Science 261 :1303; Carrell et al. (1994) Angew. Chem, Int. Ed Engl. 33:2059; Carell et al. (1994) Angew. Chem. Jnl. Ed. Engl. 33:2061; and in Gallop et al. (1994). Med Chem. 37:1233. Libraries of compounds may be presented in solution (e.g., Houghten (1992) Biotechniques 13:412-421). or on beads (Lam (1999)) Nature 354:82-84), chips (Fodor (1993) Nature 364:555-556). bacteria (Ladner USP 5,223,409), spores (Ladner USP '409), plasmids (Cull et al.(1992) Proc Natl Acad Sci USA 89:1865-1869) or on phage (Scott and Smith (1990); Science 249:386-390). Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) Proc. Natl. Acad. Sci. USA. 90:6909; Erb et al. (1994) Proc. Natl. Acad. Sci. USA 91: 11422; Zuckermann et al. (1994), J. Med. Chem. 37:2678; Cho et al. (1993), Science 261 :1303; Carrell et al. (1994) Angew. Chem Int. Ed. Engl. 33:2059, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

It is recognized by the inventors that certain therapeutic agents have been identified for cardiac, muscular, chronic pain, acute pain and other disorders, and analgesics and anesthetics that are modulators of sodium channels. Use of these sodium channel modulators

for treating epilepsy and related neurological disorders also falls within the scope of this invention. In one embodiment of this invention, sodium channel blockers are modified to achieve improved transport across the blood brain barrier in order to have direct effect on neuronal SCNA proteins and genes. Descriptions of such compounds are found at
5 Hunter, JC et al. Current Opinion in CPNS Invest. Drugs. 1999 1(1):72-81; Muir KW et al. 2000. Cerebrovasc. Disc. 10(6):431-436; Winterer, G. 2000. Pharmacopsychiatry 33(5):182-8; Clare et al. 2000. Drug. Discov. Today 5(11):506-520; Taylor CP et al. 2000. Adv. Pharmacol. 39:47-98,
10 and Pugsley MK et al. 1998. Eur. J. Pharmacol. 342(1)93-104.

It is also recognized by the inventors that compounds which modulate (i.e. either upregulate or downregulate) transcription and translation of SCNA genes are useful for treating epilepsy or related neurological disorders. According to this invention, test compounds which
15 modulate the activity of promoter elements and regulatory elements of sodium channel genes are useful for treating these disorders.

In summary, based on the disclosure herein, those skilled in the art can develop SCNA screening assays which are useful for identifying compounds which are useful for treating epilepsy and other
20 disorders which relate to potentiation of SCNA expressing cells. The assays of this invention may be developed for low-throughput, high-throughput, or ultra-high throughput screening formats.

The assays of this invention employ either natural or recombinant SCNA protein. Cell fraction or cell free screening assays for
25 modulators of SCNA biological activity can use *in situ*, purified, or purified recombinant SCNA proteins. Cell based assays can employ cells which express SCNA protein naturally, or which contain recombinant SCNA gene constructs, which constructs may optionally include inducible promoter sequences. In all cases, the biological activity of SCNA can be

directly or indirectly measured; thus modulators of SCNA biological activity can be identified. The modulators themselves may be further modified by standard combinatorial chemistry techniques to provide improved analogs of the originally identified compounds.

5 Finally, portions or fragments of the SCNA cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome and thus, locate gene regions associated with
10 genetic disease (mutations/polymorphisms) related to epilepsy or CNS disorders that involve SCNA directly or indirectly; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample.

15 The present invention is illustrated in further detail by the following non-limiting examples.

EXAMPLE 1

Molecular analysis

20 Genomic DNA was extracted from blood samples (Sambrook et al. 1989) or lymphoblastoid cell lines (Anderson and Gusella 1984) from each individual. A panel of 210 dinucleotide (CA)_n repeat polymorphic markers with high heterozygosity (75%) were chosen from the 1993-94 Généthon map (Gyapay et al. 1994). Dinucleotide markers were spaced an average of 20 cM from each other throughout
25 the 22 autosomes.

 Genotyping of microsatellite markers was accomplished by polymerase chain reaction (PCR). The reaction mixture was prepared in a total volume of 13 μ l, using 80ng genomic DNA; 1.25 μ l 10x buffer with 1.5mM MgCl₂; 0.65 μ l BSA (2.0mg/ml); 100ng of each

oligonucleotide primer; 200mM dCTP, dGTP and dTTP; 25mM dATP; 1.5mCi [35S] dATP; and 0.5units Taq DNA polymerase (Perkin-Elmer). Reaction samples were transferred to 96 well plates and were subjected to: 35 cycles of denaturation for 30 seconds at 94°C, annealing for 30 seconds at temperatures varying from 55°C to 57°C depending on the specificity of the oligonucleotide primers, and elongation for 30 seconds at 72°C. PCR reaction products were electrophoresed on 6% denaturing polyacrylamide sequencing gels.

10

EXAMPLE 2

Genetic analysis

Two-point linkage analysis was carried out using the MLINK program version 5.1 from the LINKAGE computer package (Lathrop et al. 1984). Precise values for Zmax were calculated with the ILINK program from the same computer package. Lod scores were generated based on an autosomal dominant mode of inheritance, 80% penetrance, disease gene frequency of 1:500 and allele frequencies for all allele markers calculated from the pedigree using the computer program ILINK (Lathrop et al. 1984).

20

EXAMPLE 3

Mutations in SCN1A in IGE patients

Genomic DNA from IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 2. Following PCR, SSCP analysis was performed and mutations in SCN1A were identified as follows (Figure 3): (1) Glu1238Asp; normal: GCA TTT GAA GAT ATA; patient R10191 who has an idiopathic generalized epilepsy (IGE): GCA TTT GAC GAT ATA (found in 1 of 70 IGE patients). The mutation is thus a conservative aa

25

change, in the extracellular domain between III-S1 and III-S2. Furthermore, this residue is located at the junction between the TM domain and the extracellular domain. It may thus influence gating activity. The aa change between adult and neonatal isoforms is at a similar juxta-
5 TM domain position (between I-S3 and I-S4).
(2) Ser1773Tyr; normal: ATC ATA TcC TTC CTG, patient R9049 (affected with IGE): ATC ATA TmC TTC CTG :(TCC>TAC). This mutation is in the middle of IV-S6 TM domain; found in 1/70 IGE patients, and 0/150 control subjects tested. This mutation is interesting from a biological point of view
10 for a number of reasons. First, this region of SCN gene (IV-S6) has been found to play a critical role in fast inactivation of the SCN, by mutagenesis experiments in rat SCN (McPhee et al., 1998). This is highly relevant for pathophysiology of epilepsy, since this may increase neuronal hyperexcitability. Moreover, in patients with GEFs, a mutation has been
15 found in the SCNB1 subunit, causing impairment of the fast inactivation of the SCN (Wallace et al, 1999). Finally, many of the antiepileptic drugs (e.g. phenytoin, carbamazepine) primarily act by reducing the repetitive firing of neuron, which also involves fast inactivation of the SCN.

20

EXAMPLE 4

Mutations in SCN2A in IGE patients

Genomic DNA from IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 4. Following PCR, SSCP analysis was
25 performed and mutations in SCN2A were identified as follows (Figure 5):

(1) Lys908Arg: normal: TAC AAA GAA for patient numbers always preceded by R; R9782 (Patient with IGE): TAC AGA GAA. The mutation is thus a conservative aa change, located in an extracellular domain

between TM domains IIS5 and IIS6; in 1/70 IGE patients; 0/96 normal controls. The mutation involves an important component of the SCN gene, since the S5 and S6 segments are thought to form the wall of the transmembrane pore which allows the sodium to enter the cell. This may have an influence on the gating control of the pore.

(2) Leu768Val, in individuals R8197, R9062 and R9822 (all IGE patients) (found in 3/70 IGE patients and 0/65 control subjects). The mutations is in the IV-S6 component of the sodium channel, which is important in the inactivation of the channel (see above for more detail).

10

EXAMPLE 5

Mutations in SCN3A in IGE patients

Genomic DNA from IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 6. Following PCR, SSCP analysis was performed and mutations in SCN3A were identified as follows (Figure 7):

(1) Asn43DEL: allele 1: CAA GAT AAT GAT GAT GAG ; allele 2: CAA GAT --- GAT GAT GAG ; in open reading frame deletes 1 aa: DNDDEN->QDDDEN, in the cytoplasmic N-terminal segment; in IGE patients, the frequency of allele 1 = 131/146 (0.90); allele 2 = 15/146 (0.10); for IGE patients: homozygotes (22): R3958, R9632; heterozygotes (12): R9049, R9152, R9649, R9710, R9896, R10069, R10191, R10213, R9993, R10009, R10256 . Of note, 2 patients are homozygous for the rare allele and all patients have IGE. In controls: allele 1 = 145/154 (0.94); allele 2 = 9/154 (0.06) and no 22 homozygotes were found.

(2) normal: tgggtgaaggtag, R10670 (IGE patient): tgggtataaggtag, in conserved intron between 5N & 5A exons, significance uncertain.

(3) normal: ccccttatatctccaac, R10250 (IGE patient): ccccttatayctccaac; in conserved intron between 5N & 5A exons, significance uncertain.

- (4) Val1035Ile: normal: AAA TAC GTA ATC GAT, R9269 (IGE patient): AAA TAC RTA ATC GAT ; (GTA>ATA = Val>Ile). The mutation is thus a conservative aa change which destroys a SnaBI site (this could thus be used as a polymorphism identifiable by restriction enzyme digestion). In
- 5 SCN1A, this Val is a Ile, therefore probably not a causative mutation. In cytoplasmic domain bw II-S6 & III-S1 TMs; found in 1/70 IGE alleles; and 0/70 controls.

EXAMPLE 6

10 **SCN1A is involved in idiopathic
generalized epilepsy**

- The assumption that SCN1A gene is involved in idiopathic generalised epilepsy in humans is based on many sets of evidence. First, a mutation has been found in a large Australian family
- 15 with autosomal dominant epilepsy. The phenotype is idiopathic generalised epilepsy that is associated with febrile seizures (GEFS syndrome). The gene for this family has been previously mapped to the long arm of chromosome 2. The maximum lod score is 6.83 for marker D2S111. The candidate region is very large, spanning 21cM between
- 20 markers D2S156 and D2S311. However, within this interval, there is a cluster of sodium channel genes, including SCN1A which was hypothesized to be a candidate gene for the disease.

- Screening by SSCP of a small panel of three (3) affected patients from the family, and 3 normal controls was carried-out at
- 25 first. All the exons of the SCN1A gene have been amplified by PCR, and a SSCP variant in exon 4 was found for all of the affected individuals, and none of the controls. By sequencing an affected patient and a control, an A-T substitution at nucleotide 565 was found. This variation destroys a BamHI restriction site, this enzyme was thus used as a diagnostic test to

screen all the affected patients from the family, as well as more control cases. All affected patients from the family have A565T substitution, and none of the unaffected patients in the same kindred. An A565T substitution was not found in more than 400 control chromosomes.

5 The A565T substitution correspond to a non-conservative amino acid change (D188V). This amino acid is conserved in all sodium channels thus far identified, in all species. The only exception is SCN2A identified in rat by Numa et al, where the aspartic acid is replaced by asparagine. However, it is likely that this represents
10 an error during replication of cDNA, since other investigators have cloned the same gene in rat and found that the aspartic acid is conserved at position 188. Moreover, the same group has shown that D188N has a functional effect on channel activation in oocytes (Escayg et al., *Nature Genetics*. 24(4):343-5, 2000). Of note, this A565T substitution has not
15 been found in 150 epileptic patients and in 200 control patients. Thus, this substitution has yet to be identified after 700 chromosomes assessments.

 In view of proving that D188V in SCN1A, identified in the large Australian family studied, is a pathogenic mutation, the oligonucleotide mismatch mutagenesis technique was used to introduce
20 the mutation in rat SCN1A clone. RNA was isolated from mutant and wild-type clones, and injected into oocytes in view of recording sodium currents by the patch-clamp technique. The amplitude of the currents was dramatically reduced for the mutant. Also, a small shift in the inactivation curve was observed for the mutant, as compared to the wild-type. Taken
25 together, these preliminary results confirm a functional effect of D188V mutation on SCN1A gene. (more detail below).

 The results presented herein are corroborated by studies from other investigators. For example, several other groups have also found linkage to the same locus on chromosome 2 for families with

GEFS or very similar syndromes. Mutations in SCN1A (Thr875Met mutation; Arg1648His) have been found to be the cause of the epileptic syndrome in at least two (2) of these families (Escayg et al., *Nature Genetics*. 24(4):343-5, 2000). Also, GEFS syndrome has been shown to
5 be caused by mutation in SCN1B gene. It is demonstrated that the beta subunits interact with alpha subunits of voltage-gated sodium channels to alter kinetics of sodium currents in cells. These data suggest a common mechanism for generating abnormal neuronal discharges in the brain of patients with idiopathic generalised epilepsy.

10 Finally, in the process of screening patients from the large kindred with GEFS described above, a large cohort of patients with idiopathic generalised epilepsy was also screened by SSCP. Two (2) SSCP variants, that were subsequently sequenced were thereby identified. The variation observed are shown in Table 3:

Table 3

exon	DNA variation	IGE alleles	Control alleles
1Ax17	Glu1238Asp; conservative AA change in extracellular domain between III-S1 and III-S2	3/254	0/284
1Ax24.2	Ser1773Tyr; middle of IV-S6 TM domain	1/252	0/334

Previous functional studies have shown that amino acid substitution in the IV-S6 transmembrane domain of SCN2A significantly affects the rate of inactivation of the channel. It is thus likely that Ser1773Tyr will have an effect on the SCN1A gene function. Such functional studies are currently underway.

EXAMPLE 7

Further validation of the role of SCN1A, SCN2A, SCN3A, and specific mutations thereof in IGE and epilepsy in general

A number of methods could be used to further validate the role of SCN1A, SCN2A, SCN3A, and specific mutations thereof in IGE. For example, additional patients could be screened for mutations in SCN1A, SCN2A, or SCN3A. Furthermore, additional normal patients could be screened in order to validate that the mutations identified significantly correlate with disease, as opposed to reflecting a polymorphism which is not linked to IGE. Polymorphisms which are not directly linked to IGE, if in linkage disequilibrium with a functional mutation

linked to IGE, could still be useful in diagnosis and/or prognosis assays. In addition, functional studies can be carried. Numerous methods are amenable to the skilled artisan. One particularly preferred functional assay involves the use of *Xenopus* oocytes and recombinant constructs harboring normal or mutant sequence of SCN1A, SCN2A, or SCN3A. *Xenopus* oocytes have been used in functional assays to dissect the structure-function relationship of the cyclic AMP-modulated potassium channel using recombinant KCNQ2 and KCNQ3 (Schroeder et al., 1998). As well, it has been used to dissect the structure-function relationship of the beta subunit of the sodium channel (SCN1B gene; Wallace et al. 1998).

One such example of functional studies was investigated by assessing the effects of mutation D188V in the SCN1A gene on sodium channel function by introducing the mutation into a cDNA encoding the rat ortholog SCN1A gene. This rat gene shares > 95% identity with the human SCN1A gene. The expression of wild type and mutant channels in *Xenopus* oocytes, and the examination of their properties using voltage-clamp electrophysiological recording is amenable to this *Xenopus* system. Wild type sodium channels are closed at hyperpolarized membrane potentials. In response to membrane depolarization the channels open within a few hundred microseconds, resulting in an inward sodium flux, which is terminated within a few milliseconds by channel inactivation. In whole cell recordings, rapid activation and inactivation of thousands of sodium channels distributed throughout the cell membrane results in a transient inward sodium current that rises rapidly to peak amplitude and then decays to baseline within a few milliseconds. Among the channel properties that are likely to be altered by mutations linked to epilepsy are: 1) the voltage-dependence of activation, a measure of the strength of membrane depolarization

necessary to open the channels; 2) the voltage-dependence of steady state inactivation, a measure of the fraction of channels available to open at the resting membrane potential; and 3) the time course of inactivation. Preliminary results indicate that D188V mutant channels are identical to wild type channels with respect to the voltage-dependence of activation and to inactivation time course. However, steady state inactivation for the mutant channels is shifted to membrane potentials that are slightly more positive than observed in wild type channels. This positive shift should increase the fraction of channels available to open at rest. This could increase neuronal excitability and contribute to epileptogenesis. Thus, a functional consequence of a naturally occurring mutation in a sodium channel gene has been tentatively identified. Thus, the functional consequence of the D188M mutant could at least in part explain its role in epilepsy. Such a functional consequence is expected to be observed with other mutations identified above in SCNA1, SCNA2 and SCNA3.

Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims.

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WHAT IS CLAIMED IS:

1. A method of determining an individual's predisposition to epilepsy and/or development of epilepsy, as well as
5 predicting this individual's response to medication, said method comprising the step of determining the genotype of at least one gene selected from SCN1A, SCN2A and SCN3A of the individual, or of a DNA variant, equivalent, or mutation which shows a linkage disequilibrium therewith, thereby determining an individual's predisposition to epilepsy
10 and/or development of epilepsy.

2. The method of claim 1, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises restriction endonuclease digestion.

3. The method of claim 1 or 2, wherein the step of
15 determining the SCN1A, SCN2A or SCN3A genotype comprises hybridizing with allele specific oligonucleotides.

4. The method of claim 1, which further comprises a step, prior to determining the SCN1A, SCN2A or SCN3A genotype, of amplifying a segment of the the SCN1A, SCN2A or SCN3A using
20 polymerase chain reaction.

5. The method of claim 1, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises a sequencing of SCN1A, SCN2A or SCN3A , or parts thereof.

6. The method of claim 1, wherein the SCN1A,
25 SCN2A or SCN3A genotype is determined using a polymorphic variant

site in linkage disequilibrium with at least one allelic variant or mutant identified in accordance with the present invention.

7. An assay for screening a test agent and selecting an agent which modulates inactivation of a sodium channel involved in epilepsy comprising:

a) a recombinant SCN1A, SCN2A or SCN3A gene which encodes an alpha subunit of said sodium channel or functional fragment thereof; and

b) assaying a function of said sodium channel;

wherein an agent can be selected when an observable difference is observed between the inactivation of said sodium channel in the presence of said test agent, as compared to in an absence thereof, and wherein a malfunction of said sodium channel is associated with epilepsy.

8. An assay for screening a test agent and selecting an agent which modulates the activity of a sodium channel involved in epilepsy comprising:

a) a recombinant SCN1A, SCN2A or SCN3A gene which encodes an alpha subunit of said sodium channel or functional fragment thereof; and

b) assaying the activity of said sodium channel;

wherein an agent can be selected when an observable difference is observed between the activity of said sodium channel in the presence of said test agent, as compared to in an absence thereof, and wherein a malfunction of said sodium channel is associated with epilepsy.

9. A method of using specific alleles of the SCN1A, SCN2A or SCN3A genes, or a variant, equivalent, or mutation thereof which shows linkage disequilibrium therewith, to set-up a screening assay

for agents destined to modulate sodium channel function for the purpose of identifying agents having an application in epilepsy therapy.

5 10. A method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising:

- a) providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene;
- 10 b) contacting said screening assay with a test compound; and
- c) detecting if said test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene;

wherein a test compound which modulates said biological activity is a compound with said therapeutic effect.

15

11. The method of claim 10, wherein the test compound with said therapeutic effect is further modified by combinatorial or medicinal chemistry to provide further analogs of said test compound also having said therapeutic effect.

20

12. A compound having therapeutic effect on epilepsy or other neurological disorders, identified by a method comprising;

- a) providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene;
- 25 b) contacting said screening assay with a test compound; and
- c) detecting if said test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene;

wherein a test compound which modulates said biological activity is a compound with said therapeutic effect.

13. The compound of claim 12, wherein the
5 compound with said therapeutic effect is further modified by combinatorial or medicinal chemistry to provide analogs of said compound also having said therapeutic effect.

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Ch 2q23-q31

Centromere

1cM	D2S142
	D2S284
4cM	
4cM	D2S156/
	D2S354
	D2S111
5cM	
	D2S294
2cM	
	D2S335

IGE locus

6cM		29 cM
2cM	D2S324	
2cM	D2S384	
	D2S152	
8cM		

Telomere

D2S311

FIG. 1

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1Ax00.1

NaC-340 TGTGTTCTGCCCCAGTGAGACT,
NaC-341 CTCCTGCTCTGCCCAAAGTGAAT
257 bp 53.4C

1Ax00.2

NaC-342 GGCGATGTAATGTAAGGTGCTGTC,
NaC-343 GTGCCTTCAGTTGCAATTGTTTCAG
259 bp 54.5C

1Ax01.1

NaC-268, TTAGGAATTTTCATATGCAGAATAA,
NaC-269 TGGGCCATTTTTCGTCGTC
201 bp 50.9C

1Ax01.2

NaC-270 GAAAGACGCATTGCAGAAGAAAAGG,
NaC-271 CTATTGGCATGTGTTGGTGCTACA
277 bp 54.4C

1Ax02

NaC-45 GTGCTGGTTTCTCATTTAACTTTAC,
NaC-46 TTCCCAACTTAATTTGATATTTAGC
319 bp 49.9C

1Ax03

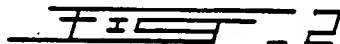
NaC-87, GCAGTTTGGGCTTTTCAATGTTAG,
NaC-88, GACACAGTTTCARAATCCCRAATG
234 bp 48.9C

1Ax04

NaC-63, TTAGGGCTACGTTTTCATTTGTATG,
NaC-64, AGCACTGATGGAAAACCAAAGTAT
338 bp 50.8C

1Ax05

NaC-164 AGCCCATGCAGTAATATAAATCCT,
NaC-165 TCCAGGCTGATAAGCTATGTCTAA
488 bp 52.8C



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1Ax06

NaC-276, CTGTGGCCTGCCTGAGCGTATT,
NaC-277 CCAATTCTACTTTTAAAGGAAATG
248 bp 50.3C

1Ax07

NaC-272, AAATACTTGTGCCTTTGAA,
NaC-273, GTACATACAATATACACAGATGC
240 bp 46.7C

1Ax08

Nac-89, AGGCAGCAGAACGACTTGTAATA,
NaC-90, ATCCGGTTTTAATTTTCACTCA
267 bp 51.9C

1Ax09.2

NaC-217 GTTGAGCACCTTAGTGAATAATA,
NaC-218 TCACACGCTCTAGACTACTTCTCT
337 bp 52.7C

1Ax10a NaC-29, TGCAAATACTTCAGCCCTTTCAA,
NaC-30, TTCCCCACCAGACTGCTCTTTC
239 bp 55.1C

1Ax10a


NaC-31, GCAGCAGGCAGGCTCTCA,
NaC-32, TCTCCCATGTTTTAATTTTCAACC
293 bp 54.5C

1Ax10b

NaC-67, ATAATCTTGCAAAATGAAATCACA,
NaC-68, ATCCGGGATGACCTACTGG
307 bp 53.7C

1Ax10b

NaC-65, GATAACGAGAGCCGTAGAGATTCC,
NaC-66, AGCCAGCCATGCCTGAACTA
282 bp 56.4C

 *2 (cont'd)*

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1Ax10c

NaC-39, TGTTTGCTTGTCATATTGCTCAA,
NaC-40, TGCACTATTCCCAACTCACAAA
286 bp 50.7C

1Ax11.1

NaC-69 AAGGGTGTCTCTGTAACAAAAATG,
NaC-70, GTGATGGCCAGGTCAACAAA
269 bp 50.8C

1Ax11.2

NaC-71 CTGGGACTGTTCTCCATATTGGTT,
NaC-72, TTTGCAGGGGCCAGGAAG
294 bp 53.3°C

1Ax12

NaC-41 CATTGTGGGAAAATAGCATAAGC,
NaC-42, GCAAGAACCCTGAATGTTAGAAA
334 bp 51.2C

1Ax13.1

NaC-92 TAATGCTTTTAAGAATCATACAAA,
NaC-93, CCAGCGTGGGAGTTGACAATC
256 bp 51.1C

1Ax13.2


NaC-75 CGGCATGCAGCTCTTTGGTA,
NaC-91, ATGTGCCATGCTGGTGTATTTC
277 bp 55.6C

1Ax14.1

NaC-79 CACCCATCTTCTAATCACTATGC,
NaC-80, CAGCAATTGAGATTATTCATT
254 bp 50.4C

1Ax14.2

NaC-81 GCAGCCACTGATGATGATAA,
NaC-82, CTGCCAGTTCCTATACCACTT
269 bp 49.4C

 (cont'd)

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1Ax14.3

NaC-83 TACAGCAGAAATTGGGAAAGAT,
NaC-84, GTATTCATACCTACCCACACCTAT
269 bp 50.2C

1Ax15

NaC-202 TTCTTGGCAGGCAACTTATTACC,
NaC-203 TAAGCTGCACTCCAAATGAAAGAT
233 bp 53.1C

1Ax16.1

NaC-187, GGCTGAATGTTTCCACAACACT,
NaC-168 GTTCAACTATTCGGAAACACG
277 bp 51.4C

1Ax16.2

NaC-188, AGGCAGAGGAAAACAATGG,
NaC-189, ACAAGGTGGGATAATTAAAAATG
234 bp 50.3C

1Ax17

NaC-143, GTTTCTCTGCCCTCCTATTCC,
NaC-144, AAGCTACCTTGAACAGAGACA
330 bp 48.8C

1Ax18

NaC-139, AATGATGATTCTGTTTATTA,
NaC-140, AATTGCCATTCCTTTTG
272 bp 46.1C

1Ax19.1

NaC-219 TTGACATCGAAGACGTGAATAATC,
NaC-220 CCATCTGGGCTCATAAACTTGTA
285 bp 49.3C

1Ax20

NaC-338 CCCTTTGAAAATTATATCAGTAA,
NaC-339 ATTTGGTCGTTTATGCTTTATTC
230 bp 47.6C

FIG - 2 (cont'd)

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1Ax21

NaC-252, TCCAGCACTAAAATGTATGGTAAT,
NaC-253, ATTTGGCAGAGAAAACACTCC
261 bp 49.8C

1Ax22

NaC-254, TTTTAGCCATCCATTTTCTATTTT,
NaC-255, TATTTTCCCCCATATCATTGGA
223 bp 49.1C

1Ax23.1

NaC-256 TTGCAAGAACTAGAAAGTC,
NaC-257 TTGATGCGTGACAAAATGG
250 bp 48.3C

1Ax23.2

NaC-258 GACCAGAGTGAATATGTGACTACC,
NaC-259 CTGGGATGATCTTGAATCTAATC
246 bp 49.5C

1Ax24.1

NaC-221 GCAACTCAGTTCATGGAATTTGAA,
NaC-222 CTTGTTTTCGTTTTAAAGTAGTA
289 bp 56.1C

1Ax24.2


NaC-213 CAAAGATCACCTGGAAGCTCAGTT,
NaC-223 TTCAAGCGCAGCTGCAAAGTGAAT
277 bp 55.8C

1Ax24.3

NaC-260 ACATCGGCCTCCTACTCTTCCTA,
NaC-261 ACAGATGGGTCCCACAGTCC
268 bp 55.3C

1Ax24.4

NaC-262 TAACGCATGATTTCTTCACTGGTT,
NaC-263 ATCCCAAAGATGGCGTAGATGA
262 bp 54.9C

 - 2 (cont'd)

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1Ax24.5

NaC-308, TGAGAAATAGGCTAAGGACCTCTA,

NaC-309 CCTAGGGGCTGGATTCC

244 bp 53.2C

1Ax24.6

NaC-310, AAGGGGTGCAAACCTGTGATTTT,

NaC-311 AGGGCCATGTGGTTGCCATAC

252 bp 53.4C

1Ax24.7

NaC-312 CTTCCGGTTTATGTTTTCAATTTCT,

NaC-313 TCTTTATTAGTTTTGCACATTTTA

278 bp 48.4C

1Ax24.8

NaC-364 CAATCCTTCCAAGGTCTCCTATC,

NaC-365 TTTCATCTTTGCCTTCTTGCTCAT

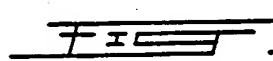
326 bp 52.4C

1Ax24.9

NaC-366 CATGTCCACTGCAGCTTGTCCA,

NaC-367 TCCCCTTTACACAGAGTCACAGTT

292 bp 53.1C

 (cont'd)

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a. Glu1238Asp:

normal:

GCA TTT GAA GAT ATA;

patient R10191 with IGE:

GCA TTT GAC GAT ATA.

b. Ser1773Tyr:

normal:

ATC ATA TcC TTC CTG;

patient R9049 with IGE:

ATC ATA TmC TTC CTG; TCC>TAC

FIG. 3

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2Ax00.1 NaC-235 ATGGGTTGAATGACTTTCTGACAT, NaC-236,
AGGCATTTTCCTGTACAGGGACTAC
266 bp 52.7C

2Ax00.2 NaC-237 ACAGGAAATGCCTCTTCTTACTTC, NaC-238,
TTTCCCAAGGATTCTACTACTGT
277 bp 50.6C

2Ax01 NaC-100, AGTGCATGTAACTGACACAATCAC, NaC-101,
CTTGCGTTCCTGTTTGGGTCTCT
241 bp 53.7C

2Ax01 NaC-11 TCCGCTTCTTTACCAGGGAATC, NaC-102,
AGGCAGTGAAGGCAACTTGACTAA
259 bp 55.1C

2Ax02 NaC-96, CAGGGCAATATTTATAAATAATGG, NaC-97,
TTTGGAATAATGTGTAGCTCAATAA
289 bp 48.7C

2Ax03 NaC-43, AAGGCATGGTAGTGCATAAAAG, NaC-44,
ATGAAACATAAAGGGAGGTCAA
201 bp 49.3°C

2Ax04 NaC-47, AATGTGAGCTTGGCTATTGTCTCT, NaC-48,
ATAGGCTCCCACCAGTGATTAC
213 bp 50.9°C

2Ax05 NaC-49, AGGCCCCTTATATCTCCAAGT, NaC-50,
CAACAAGGCTTCTGCACAAAAG
241 bp 53.9°C

2Ax05.2 NaC-110, CTTGGTGGCTTGCCTTGAC, NaC-111,
TCATGAGTGTCGCCATCAGC
223 bp 51.1C

FIG - 4

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2Ax05.3 NaC-112, GGAAAGCTGATGGCGACACT, NaC-113,
CTGAGACATTGCCCAGGTCC
329 bp 53.0C

2Ax05.4 NaC-114, TTTTACCCGTTGCTTTCTTTA, NaC-115,
TATCCCTTGCTCTTTCATTTATCT
224 bp 50.9C

2Ax06.1 NaC-169, GCCGGTAAAATAGCTGTTGAGTAG, NaC-170,
GCCATTGCAAACATTTATTTTCGTA
206 bp 53.3C

2Ax06.2 NaC-171, GCGTGTTTGCGCTAATAG, NaC-172,
CTAAGTCACTTGATTCACATCTAA
295 bp 48.0C

2Ax07 NaC-196, ACAGGGTGGCTGAAGTGTTTA, NaC-197,
GTGGGAGGTGGCAGGTTATT
199 bp 52.6C

2Ax08 NaC-118, CAATTAGCAGACTTGCCGTTATT, NaC-119,
TCTCTTGAGTTCGGTGTTTTATGA
252 bp 52.9C

2Ax09 NaC-120, ACCGA ACTCAAGAGAATTGCTGTA, NaC-121,
AAAGGACCGTATGCTTGTTCACTA
334 bp 52.9C

2Ax10a.1 NaC-161 TATGAATGCGCATTTTACTCTTTG, NaC-156,
TGGAGCTCAACTTAGATGCTACTG
286 bp 52.1C

2Ax10a.2 NaC-13 GGTGCTGGTGGGATAGGAGTTTTT, NaC-162,
TCCATTAAATTCTGGCATATTCTT
316 bp 50.9C

2Ax10b.1 NaC-145 TCAGAGGGGTGCTTTCTTCCACAT, NaC-14,
CTTCGGCTGTCATTGTCCTCAAAG
298 bp 55.6C

Ex 4 (cont'd)

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2Ax10b.2 NaC-146, GCAAAGGACATTGGCTCTGAGAAT, NaC-147,
CTGCCTGCACCAGTCACAACCTCT

324 bp 59.4C

2Ax10c NaC-190, TGGGCTTTGCTGCTTTCAA, NaC-191,
AGTAACTGTGACGCAGGACTTTTA

218 bp 51.5C

2Ax11.1 NaC-148, CCCTGTTCTCCAGCAGATTA, NaC-70,
GTGATGGCCAGGTCAACAAA

283 bp 51.5C

2Ax11.2 NaC-149, TTTGATTTGGGACTGTTGTAAAC, NaC-150,
AAGGCAATTATAAACTCTTTCAAG

233 bp 52.0C

2Ax12 NaC-159, TGGGAGTTAAATTAAGTTGCTCAA, NaC-160,
ACATTTTATGAACACTCCCAGTTA

285 bp 50.4C

2Ax13.1 NaC-239 ATTAACACTGTTCTTGCTTTTAT, NaC-240,
GTGCCAGCGTGGGAGTTC

239 bp 51.1C

2Ax13.2 NaC-241 GTGGGGGCTCTAGGAAACCT, NaC-242,
TTTAATGAAAATGAGGAAAATGTT

324 bp 53.7C

2Ax14.1 NaC-134, GACCAAGCATTTTTATTTTCATTC, NaC-135,
AGTGGCAGCAAGATTGTCA

234 bp 49.6C

2Ax14.2 NaC-136, GGCCTTGCTTTTGAGTTCC, NaC-137,
GGTCTTTGCCTATTTCTATGGTG

257 bp 51.1C

FIG - 4 (cont'd)

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2Ax14.3 NaC-266, TTAAACCGCTTGAAGATCTAAATA, NaC-267,
TATACACCAAAATATCTCCTTAT
319 bp 48.5C

2Ax15 NaC-314 GGGGCACACCTAATTAATTTTTAT, NaC-315,
AAAGAGGATACTCAAGACCACATA
(247 bp) 51.5C

2Ax16 NaC-344 CCCACCAACACAAATATACCTAAT, NaC-345,
TGAAGGGAAAGGGAAAAGATT
283 bp 52.2C

2Ax17 NaC-346 TCCAGCCTTAGGCACCTGATAA, NaC-347,
ATAAAGCAGCAAAGTGCAGCATAC
310 bp 52.4C

2Ax18 NaC-348 AAGGCTGAACTGTGTAGACATTTT, NaC-349,
TGACATTTCCATGGTACAAAGTGT
262 bp 52.2C

2Ax19.1 NaC-350 TTTGTTGTTGGCTTTTCACTTAT, NaC-351,
CCACCTGGCAGTTTGATTG
268 bp 51.9C

2Ax19.2 NaC-352 TAAGCGTGGTCAACAACACTACAGT, NaC-353,
ATTCTTGCCAGCATTTATTGTC
260 bp 50.2C

2Ax20 NaC-354 CAAAACATTGCCCCAAAAG, NaC-355,
TCAAATAAACAATTTCCCTCTAA
239 bp 48.1C

2Ax21 NaC-306, GATAATTAAAACTCACTGATGTA, NaC-307,
GGAGGCTAAAGGAAAGAGTATG
288 bp 46.6C

2Ax22 NaC-356 ATTTTATAGCCAGCAAAGAACAC, NaC-357,
CTAGAAATTCGGGCTGTGAA
230 bp 49.6C

Exhibit - 4 (cont'd)

SUBSTITUTE SHEET (RULE 26)

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2Ax23.1 NaC-358 CTGCTTTGTGACCTAAGGCAAGTT, NaC-359,
GTGACCATGTTAAGGCAGATGAGG
290 bp 51.4C

2Ax23.2 NaC-360 GGAATGGTCTTTGATTTTGTAACC, NaC-361,
TCCTTAACCTGAATAAAAGCACCTC
290 bp 51.6C

2Ax24.1 NaC-207 TGGAACACCCATCAAAGAAGATACT, NaC-208,
GTGGGAGTCCTGTTGACACAAAC
278 bp 52.8C

2Ax24.2 NaC-209 AGCGATTTCATGGCATCAAAC, NaC-210,
ACGTGGTGGAAGGCGTCATA
270 bp 52.9C

2Ax24.3 NaC-211 GCGACCCAGTTTATAGAGTTTGCC, NaC-212,
CTTGTTTGCGTTTCAACGTGGTC
289 bp 56.1C

2Ax24.4 NaC-213 CAAAGATCACCCCTGGAAGCTCAGTT, NaC-214,
ATCCAGGGCATCTGCAAAATCAGAA
277 bp 55.8C

2Ax24.5 NaC-215 TGCCTATGTTAAGAGGGGAAGTTGGG, NaC-216,
ATGACCGCGATGTACATGTTCAG
279 bp 55.3C

2Ax24.6 NaC-278 TCAATTGTTTACAGCCCGTGATG, NaC-279,
TTTATACAAAGGCAGACAACAT
302 bp 52.0C

2Ax24.7 NaC-280 AGGCGTAATGGCTACTCAGACGA, NaC-281,
GTAATCCCTCTCCCCGAACATAAAC
251 bp 53.8C

2Ax24.8 NaC-282 TTTGATTACGGGGTTGTTTACTCTTA, NaC-283,
TTCTATGGAACATTTACAGGCACATT
294 bp 52.1C

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2Ax24.9 NaC-284 TAATGTGCCTGTAAATGTTCCATAGA, NaC-285,
CAGGCTTCTTAGAAAGGACTGATAGG
264 bp 50.6C

2Ax24.10 NaC-286 GTCCCAGCAGCATGACTATC, NaC-287,
CCCCTGGGTAAAATTACTAAC
249 bp 49.4C

2Ax24.11 NaC-288 TAGCCATCTTCTGCTCTTGGT, NaC-289,
TGGCTTCCCATATTAGACTTCTG
307 bp 51.3C

2Ax24.12 NaC-290 TCTTGCCTATGCTGCTGTATCTTA, NaC-291,
AGTCGGGCTTTTCATCATTGAG
207 bp 51.8C

2Ax24.13 NaC-292 TTCTTCATGTCATTAAGCAATAGG, NaC-293,
TTCAATTATAAAAGTGCTAGGAACA
299 bp 49.4C

2Ax24.14 NaC-294 CTTTCAGGTGGATGTCACAGTCACTA, NaC-295,
ATTCAAGCAATGCCAAGAGTATCA
263 bp 51.5C

2Ax24.15 NaC-296 CTTTCAATAGTAATGCCTTATCAT, NaC-297,
TCCTGCATGCATTTACCAAC
348 bp 49.6C

2Ax24.16 NaC-362 CTGTTACATTTTGTA AAACTAAT, NaC-263,
ATCCCAAAGATGGCGTAGATGA
309 bp 50.8C

2Ax24.17 NaC-325 CACGCTGCTCTTTGCTTTGA, NaC-363,
GATCTTTGTCAGGGTCACAGTCT
269 bp 54.0C

FIG. 4 (cont'd)

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a. Lys908Arg:

normal:

TAC AAA GAA;

9782 (Patient with IGE):

TAC AGA GAA;

b. leu768val, in individuals 8197, 9062 et 9822 (all IGE patients).

FIG. 5

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3Ax00a.1 NaC-390 TGTGTCCGCCAGTAGATGG, NaC-391,
TTTTTGACCACAGAGGTTTACAA
233 bp 51.4C

3Ax00a.2 NaC-392 GAAGCGGAGGCATAAGCAGA, NaC-393,
GGTGCAGATAATGAAATGTTTTGT
253 bp 51.3C

3Ax00b NaC-394 CACCCCTATGCCAAATGTCAAAGA, NaC-395,
CAAAAACAAACTTATACCCAGAAG
293 bp 51.6C

3Ax00c NaC-396 CAAATATTGGGCAAACCCTAAT, NaC-397,
AAGGTGCCATCACAAAATCAT
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3Ax01.1 NaC-51 ATCGCTTGCTTTCCTAACTCTTGT, NaC-52,
AAGTCACTATTTGGCTTTGGTTG
260 bp 53.1C

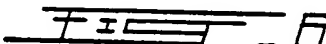
3Ax01.2 NaC-53 AGAAGCCCCAAAAAGGAACAAGATA, NaC-54,
GGCCCAGAAAAGTATATTACAGTT
231 bp 50.8C

3Ax02 NaC-85, TCCTTAAATAAGCCCATGTCTAAT, NaC-86,
TCTCAAAGAAATTTTACAGATACT
273 bp 47.3C

3Ax03 NaC-27, AATGGCCATGGTAACCTACTAACA, NaC-28,
CAGGCTATACCCACAAGGAGATT
212 bp 51.8C

3Ax04 NaC-94, TGTTAATTTTGGCTTGGATGTT, NaC-95,
TCACTCCTTTGCGCTTATCAA
198 bp 50.8C

3Ax05.1 NaC-247, AGGGCTCTATGTGCCAAACC, NaC-248,
AGGGGCCTACTACCTTACACCAG
213 bp 52.2C



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3Ax05.2 NaC-249 TGTAATCCCAGGTAAGAAGAAAC, NaC-250,
TACCGGGATGAACTGTAATAATAA
304 bp 51.8C

3Ax06.1 NaC-192, TTCTGGCACTCTTCCTCAGGTAAC, NaC-193,
GTCCCATTTGAATCCATTGTGC
261 bp 55.4C

3Ax06.2 NaC-194, GGCCCCCAAGCGATTCTG, NaC-195,
TGTACACCCACAGTCTCAACTATT
209 bp 50.3C

3Ax07 NaC-204, ACAGCCACCTTTGTAAATAA, NaC-205,
TTTTTCGCAAAGAGTTCTAT
220 bp 46.6C

3Ax08 NaC-98, AAAGTGACCCTACCTCCATTTCTC, NaC-99,
ACTCAGCCTATGCTTTTCATTTC
247 bp 53.2C

3Ax09 NaC-37 CAGATATTTATTTGGGGACATTAT, NaC-38,
AAATCTTTGCKTTTATCACTCAGT
295 bp 52.0C

3Ax10a.1 NaC-198 TAGTGCCTGGCTTTGTTTTATGAC, NaC-199,
CGGATTTGGGAAAGCTGTCTCT
225 bp 54.3C

3Ax10a.2 NaC-200 AGAGCACCTTGAAGGAAACAACAA, NaC-274,
TCCCTCAACTGAAGTACAGATAGT
253 bp 51.2C

3Ax10b NaC-33, ATAATTGCGTTCTTCCCCTACCC, NaC-34,
AAGCCCTGGCACCATCCTG
301 bp 56.2°C

3Ax10c NaC-35, TTTGCAAAGAAATGCTATGT, NaC-36,
CTGGGTAAACAGACTTCAGTAAT
303 bp 51.4°C

FI - 6 (cont'd)

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3Ax11.1 NaC-122, ATGGGATTGTCTTCTCAAGTTTCT, NaC-123,
GATGGCAAGATCAACAAATGGA
294 bp 50.3C

3Ax11.2 NaC-124, CTTGATCTGGGACTGCTGTGATG, NaC-125,
AGGATATAATTTTGGTTCAACA
284 bp 51.5C

3Ax12 NaC-61, TTTTCAGTGCTCTTGATAGTAGTG, NaC-62,
GTGCCAATGAGCGACAGG
254 bp 50.7°C

3Ax13.1 NaC-73, CCACGTGTGGTTCTATGATACC, NaC-74,
ACCGTGGGAGCGTACAGTCA
298 bp 52.3C

3Ax13.2 NaC-75, CGGCATGCAGCTCTTTGGTA, NaC-76,
TGGCCACGTTCCCTAGCTACTGTC
291 bp 55.9C


3Ax14.1 NaC-55, GAGTTCCCTTTTTAGGCTGTTATT, NaC-56,
TCTTATTGCCTTCATGGATTCTA
285 bp 50.5C

3Ax14.2 NaC-57, TGAAAAATAAGATGCGGGAGTG, NaC-58,
GTGAGGCTGGGGTTGTTTATG
247 bp 51.7C

3Ax14.3 NaC-59, GAGATGGGAATGGAACCACCA, NaC-60,
TTCGATAATGCATATAAGCACAA
297 bp 51.7C

3Ax15 NaC-318 AAGGGGGAAAATCACATCTTT, NaC-319,
TTAAATGAGGCATATTCAGTCTCC
235 bp 51.8C

3Ax16 NaC-116, GGAAGTGGAGTGGGGAAGG, NaC-117,
ATTCTTGCCAATATGCATTCACT
271 bp 51.1C

 (cont'd)

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3Ax17 NaC-157, TTCTTTTGTACTCACTATTATACTAA, NaC-158,
AAACTTGCCTCTTTTAAAAACAAT
317 bp 46.6C

3Ax18 NaC-374 TACCACACCCTATACCTTCAGTCA, NaC-375,
GAGTATGGCACCCCTTTTCTATCTA
275 bp 51.4C

3Ax19.1 NaC-386 GCTATGTTCCCCTCGCTGTCT, NaC-387,
TGCTTGCCAAGAGCCTGAC
231 bp 53.6C

3Ax19.2 NaC-388 GCTGGCAAGTTCTACCACTGTG, NaC-389,
CAAACGAAGAACATCAGGGAAATA
247 bp 53.0C

3Ax20 NaC-376 TTCACAATATTGTACAAAAAGTTA, NaC-377,
ATTACCACCAATATTCACCATAAG
230 bp 46.4C

3Ax21 NaC-378 TCAGGGTAAGGCAAAAAGTAGCAC, NaC-379,
GAACCCCAGAATGAAGAAAGGTAA
294 bp 50.2C

3Ax22 NaC-380 TTTGTGAAAGTACTATTGGAACAC, NaC-381,
ACGCATGGCTTTGGAACAT
204 bp 49.6C

3Ax23.1 NaC-382 CCCGTATGTGGAAGGGCTTTAT, NaC-383,
CTAGGTTGATCCGGGACAAAATA
246 bp 52.9C

3Ax23.2 NaC-384 AACGGATGACCAGGGCAAATAC, NaC-385,
CTAGAAGGTCCTGGGGCAACTG
234 bp 54.8C

3Ax24.1 NaC-317 AAGCCATCATGTAAAGTGAAAAG, NaC-320,
ATCCCAAAGATGGCATAGATA
274 bp 52.5C

FI - B (cont'd)

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3Ax24.2 NaC-325 CACGCTGCTCTTTGCTTTGA, NaC-326,
TGAGCTGCCAGGGTGAATTG
282 bp 54.9C

3Ax24.3 NaC-327 TTGCTAGCACCTATTCTTAATAGTGC NaC-328,
CCAGGGCAGCTGCAAAATCAGAG
318 bp 54.2C

3Ax24.4 NaC-329 CCCGATGCGACCCAGTTTA, NaC-330,
TGGAGGGGTTTGATGCCATA
250 bp 55.2C

3Ax24.5 NaC-331 GATGGATGCCCTTCGAATACAGA, NaC-332,
TTCCCATTTAGTTTGTCATAATC
258 bp 50.6C

3Ax24.6 NaC-321 AAGGGGAGGATTGACTTACCTAT, NaC-333,
TTGGCATGGACCTCCTCTTGA
302 bp 51.5C

FI - E (*cont'd*)

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a. Asn43DEL:

9706 (allele 1; IGE patient): CAA GAT AAT GAT GAT GAG ;

9632 (allele 2; patient has IGE): CAA GAT --- GAT GAT GAG ;

allele 1 = 131/146 (0.90);

allele 2 = 15/146 (0.10);

for IGE patients: homozygotes (22): 3958, 9632; heterozygotes (12): 9049, 9152, 9649, 9710, 9896, 10069, 10191, 10213, 9993, 10009, 10256 (note that 2 patients are homozygous for the rare allele; all patients have IGE); in controls: allele 1 = 45/154 (0.94); allele 2 = 9/154 (0.06) and no 22 homozygotes found.

b. normal: tggtgtaaggtag,

10670 (IGE patient): tggataaggtag

c. normal: ccccttatctccaac,

10250 (IGE patient): ccccttatayctccaac;

d. Val1035Ile:

normal: AAA TAC GTA ATC GAT,

9269 (IGE patient): AAA TAC RTA ATC GAT; GTA>ATA = Val>Ile.

FIG. 7

SEQUENCE LISTING

<110> McGill University
 Rouleau, Guy A.
 Lafrenière, Ronald G.
 Cossette, Patrick
 Ragsdale, David

<120> LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY, MUTATIONS
 THEREOF AND METHOD USING SAME TO ASSESS, DIAGNOSE,
 PROGNOSIS OR OR TREAT EPILEPSY

<130> 13180.17

<140> PCT/CA00/01404

<141> 2000-11-24

<160> 408

<170> PatentIn Ver. 2.1

<210> 1

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1205	1210	1215
His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu Leu Ser Ser		
1220	1225	1230
Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Asp Gln Arg Lys Thr Ile		
1235	1240	1245
Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr Ile Phe Ile		
1250	1255	1260
Leu Glu Met Leu Leu Lys Trp Val Ala Tyr Gly Tyr Gln Thr Tyr Phe		
1265	1270	1275 1280
Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp Val Ser Leu		
1285	1290	1295
Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr Ser Glu Leu Gly Ala Ile		
1300	1305	1310
Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg Pro Leu Arg Ala Leu Ser		
1315	1320	1325
Arg Phe Glu Gly Met Arg Val Val Val Asn Ala Leu Leu Gly Ala Ile		
1330	1335	1340
Pro Ser Ile Met Asn Val Leu Leu Val Cys Leu Ile Phe Trp Leu Ile		

1345 1350 1355 1360
 Phe Ser Ile Met Gly Val Asn Leu Phe Ala Gly Lys Phe Tyr His Cys
 1365 1370 1375
 Ile Asn Thr Thr Thr Gly Asp Arg Phe Asp Ile Glu Asp Val Asn Asn
 1380 1385 1390
 His Thr Asp Cys Leu Lys Leu Ile Glu Arg Asn Glu Thr Ala Arg Trp
 1395 1400 1405
 Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Phe Gly Tyr Leu Ser
 1410 1415 1420
 Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala
 1425 1430 1435 1440
 Ala Val Asp Ser Arg Asn Val Glu Leu Gln Pro Lys Tyr Glu Glu Ser
 1445 1450 1455
 Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe
 1460 1465 1470
 Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln
 1475 1480 1485
 Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu Gln
 1490 1495 1500
 Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys Pro Gln
 1505 1510 1515 1520
 Lys Pro Ile Pro Arg Pro Gly Asn Lys Phe Gln Gly Met Val Phe Asp
 1525 1530 1535
 Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met Ile Leu Ile Cys
 1540 1545 1550
 Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Ser Glu Tyr
 1555 1560 1565
 Val Thr Thr Ile Leu Ser Arg Ile Asn Leu Val Phe Ile Val Leu Phe
 1570 1575 1580
 Thr Gly Glu Cys Val Leu Lys Leu Ile Ser Leu Arg His Tyr Tyr Phe
 1585 1590 1595 1600
 Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile

1605	1610	1615
Val Gly Met Phe Leu Ala Glu Leu Ile Glu Lys Tyr Phe Val Ser Pro 1620	1625	1630
Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg 1635	1640	1645
Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met 1650	1655	1660
Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe Leu Val 1665	1670	1675 1680
Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala Tyr Val Lys 1685	1690	1695
Arg Glu Val Gly Ile Asp Asp Met Phe Asn Phe Glu Thr Phe Gly Asn 1700	1705	1710
Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp Gly 1715	1720	1725
Leu Leu Ala Pro Ile Leu Asn Ser Lys Pro Pro Asp Cys Asp Pro Asn 1730	1735	1740
Lys Val Asn Pro Gly Ser Ser Val Lys Gly Asp Cys Gly Asn Pro Ser 1745	1750	1755 1760
Val Gly Ile Phe Phe Phe Val Ser Tyr Ile Ile Ile Ser Phe Leu Val 1765	1770	1775
Val Val Asn Met Tyr Ile Ala Val Ile Leu Glu Asn Phe Ser Val Ala 1780	1785	1790
Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu Asp Asp Phe Glu Met Phe 1795	1800	1805
Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Met Glu 1810	1815	1820
Phe Glu Lys Leu Ser Gln Phe Ala Ala Ala Leu Glu Pro Pro Leu Asn 1825	1830	1835 1840
Leu Pro Gln Pro Asn Lys Leu Gln Leu Ile Ala Met Asp Leu Pro Met 1845	1850	1855
Val Ser Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr		

1860 1865 1870
 Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln
 1875 1880 1885
 Met Glu Glu Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Gln
 1890 1895 1900
 Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Val
 1905 1910 1915 1920
 Ile Ile Gln Arg Ala Tyr Arg Arg His Leu Leu Lys Arg Thr Val Lys
 1925 1930 1935
 Gln Ala Ser Phe Thr Tyr Asn Lys Asn Lys Ile Lys Gly Gly Ala Asn
 1940 1945 1950
 Leu Leu Ile Lys Glu Asp Met Ile Ile Asp Arg Ile Asn Glu Asn Ser
 1955 1960 1965
 Ile Thr Glu Lys Thr Asp Leu Thr Met Ser Thr Ala Ala Cys Pro Pro
 1970 1975 1980
 Ser Tyr Asp Arg Val Thr Lys Pro Ile Val Glu Lys His Glu Gln Glu
 1985 1990 1995 2000
 Gly Lys Asp Glu Lys Ala Lys Gly Lys
 2005

<210> 4

<211> 1246

<212> DNA

<213> Homo sapiens

<400> 4

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 ngnsarttrvr aktsvgktvg asvkksdvmv vcsvagmgnr nkcwnashs kntvnyngtn 180
 tvdwsydsr yhygdacgns sdagcgymcv kagrnnnygt sdtswasrmt dwnytraagk 240
 tymvvgssyna vvamaynata kamkkaaaat atashrsaa grsdsssask ssksakrrnr 300
 rkkrrksggk ddkssdsrrk grsgnrtykr ysshssrgss rrnsrtssrg rakdvgsnda 360
 ddhstdnsrr dsrrrhgrn snstsrssrm avangknhst vdcngvsvg gsvtsvgvdk 420
 atddngtttt mrkrrssshv smddsrrams astntvsrkc cwyksnwcds ywkvkhvvnv 480
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 vkakswtnmk gnsvgagntv avavvgmgks ykdcvckasd crwhmndhsv rvcgwtmwdc 600
 mvagamctvm mvmvgnvna sssadnaatd ddhmnnavdr mhkgvayvkr kysrkkdkdd 660
 nnkkdscmsn htagkddykd vngttsgggtg ssvkydsdym snnstvtvav gsdnntdsss 720

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dskknsssss gstv dgavvv tactgcvrkc cnvgrgkwwn rrtcrvhnwt vmssgaadyd 780.
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vvnagasmnv vcwsmgvnag kyhcntttgd rddvnnhtdc krntarwknv kvndnvggys 900
vatkgwmdmy aavdsrnvky symyyvgstn gvdnnkkkgg dmtkkyynam kkgskkkrgn 960
kgmvdvtrvd smcnmvtmmv tddsyvttsr nvvtgcvkxr hyytgwndvv vsvgmakyvs 1020
trvrargrrk gakgrtamms angvmyagms nayvkrvgdd mntgnsmtt sagwdgansk 1080
dcdnkvnsgs vkgdcgns vgvsyvvvnmv avnsvatsas ddmvkwkdda tmksaaannk 1140
amdmsvsgdrh cdatkrvgsg mdarmmasn skvsytttkr kvsavrayrr hkrtvkasty 1200
nknkkggank dmdrnnstkt dtmstaacsy drvtkvkhgk dkakgk 1246

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<210> 5

<211> 850

<212> DNA

<213> Homo sapiens

<400> 5

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gcaaggagaa gcaatactgg gagattacag agaagaaagg aaaaaaggct gagagaaaag 180
aggttgagga agaaatcata aatctggatt gtgagaaagt gtttaatat tagccactag 240
atggcgatgt aatgtaaggt gctgtcttga cttttttttt ttttttttga aacaagctat 300
ttgctgattt gtattaggta ccatagagtg aggcgaggat gaagccgaga agatactgca 360
gaggtctctg gtgcatgtgt gtatgtgtgc gtttgtgtgt gtttgtgtgt ctgtgtgttc 420
tgccccagtg agactgcagc ccttgtaaat actttgacac cttttgcaag aaggaatctg 480
aacaattgca actgaaggca cattgttatc atctcgtctt tgggtgatgc tgttcctcac 540
tgcagatgga taattttcct tttaatcagg taagccatct aattgtttca tcttgatttt 600
aagtttattc attccagtta ttcttttga aaaagagtcc atggaaattc agtttgggca 660
gagcaggaag tccatttttg tatgtgtatt cagaccaact gtccccctcc tccctctcct 720
cctcttcttg tccccctccc cgcgcctcc tctctcaacc ttccatgaac tgaaatcagg 780
tttgttttgc agttcagcat ttgatagaa gatgggatc tttggcctga aatagcttgg 840
catctggcca 850

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<210> 6

<211> 483

<212> DNA

<213> Homo sapiens

<400> 6

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gaataaatgg taattaaaat gtgcaggatg acaagatgga gcaaacagtg cttgtaccac 120
caggacctga cagcttcaac ttcttcacca gagaatctct tgcggctatt gaaagacgca 180
ttgcagaaga aaaggcaaag aatcccaaac cagacaaaaa aagatgacga cgaaaaatgg 240
cccaaagcaa atagtgactt ggaagctgga aagaaccttc catttattta tggagacatt 300
cctccagaga tgggtgtcaga gccctggag gacctggacc cctactatat caataagaaa 360
gtgagtgttt tttttatcag gcatattttt gctgctaatt gcctactgca ttccttgga 420
tggtgtagca ccaacacatg ccaatagcac aaatctagta tctctgttag aatgaacaca 480

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ttt

483

<210> 7

<211> 497

<212> DNA

<213> Homo sapiens

<400> 7

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tggtttctca tttaacttta caataattta ttatgacaag taacagaaag tagataacag 120
agtttaagtg gtttatactt tcatacttct atgttggtgtt cctgtcttac agacttttat 180
agtattgaat aaagggaagg ccatcttccg gttcagtgcc acctctgccc tgtacatttt 240
aactcccttc aatcctctta ggaaaatagc tattaagatt ttggtacatt catatccttt 300
ttcaagtgat taatattaac tatttgtaca tgatctgtaa gcactttata gctaaatata 360
aaattaagtt gggaaatgtc catattatat aggtttcatc actctcattt tgcattctttg 420
tcatattagc ctcatcttta aagttcatta atcacataga cattactgaa acatgtactc 480
tttaacattt tatatat

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497

<210> 8

<211> 501

<212> DNA

<213> Homo sapiens

<400> 8

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tatccctgaa ttttggttaa gctgcagttt gggcttttca atgtagctt tttgtaatat 180
aacacttgga ttttgatttt cttttgtgtg ttcttaaca ataacctaca ttattcagca 240
tgctaattat gtgcactatt ttgacaaact gtgtgtttat gacaatgagt aacctcctg 300
attggacaaa gaatgtagag taagttcaac ttatatTTTT aataacatat atacattygg 360
gattytgaaa ctgtgtctta atgtagtctt aaaataaaac tgaagagcat tttattaaag 420
tcattcctag acaaaattac gcagcaagag gacaatgctc attggccctc aggctgtgtg 480
gcgttatact gattatcact c

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501

<210> 9

<211> 563

<212> DNA

<213> Homo sapiens

<400> 9

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gctaaataga tttcatatac cttgtatttc tcacactact ctttaagacac tttacgaaac 60
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aaaatccatc tgcttagttt tcttttttag tatttatcta ttccactgat ggagtataa 180
gaaattggta tgctatgaaa aaacactgtt actttatcaa attttttgga tgcttgtttt 240
cagatacacc ttcacaggaa tatatacttt tgaatcactt ataaaaatta ttgcaagggg 300

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attctgttta gaagatttta ctttccttcg ggatccatgg aactggctcg atttcactgt 360.
cattacattt gcgtaagtgc ctttbytgaa actttaagag agaacatagt ttggttttcc 420
atcagtgcct atgcttttaa gaatagggtt gctttacctg tagaatattt ttgtgtgatt 480
tatacattca aactctggat ttcaatttag cacaacaaag gtctaagtgg aatttcacta 540
tagcatgaag gctttgcagt agt                                     563

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<210> 10

<211> 253

<212> DNA

<213> Homo sapiens

<400> 10

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cttataagcc catgcagtaa tataaatcct gctaaaatct tgaataattc tgatttaatt 60
ctacagggtt gtaacagaat ttgtaaacct aggcaatttt tcagctcttc gcactttcag 120
agtcttgaga gctttgaaaa ctatttcggt aattccagggt aagaagtgat tagagtaaag 180
gataggctct ttgtacctac agctttttct ttgtgtcctg tttttgtgtt tgtgtgtgaa 240
ctcccgctta cag                                     253

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<210> 11

<211> 340

<212> DNA

<213> Homo sapiens

<400> 11

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gtaagaagtg attagagtaa aggataggct ctttgtacct acagcttttt ctttgtgtcc 60
tgtttttgtg ttgtgtgtg aactcccgct tacaggtagc tcacagagtt tgtggacctg 120
ggcaatgtct cggcattgag aacattcaga gttctccgag cattgaagac gatttcagtc 180
attccagggt agagcaagggt tagataatga gacggacca tcagtgtgatt cagcatcctt 240
ctctgcttga cattcagttt tacagaaaat caggaatcat aagactagggt gttcaaagaa 300
atgattatta tgtagacat agcttatcag cctggagtta                                     340

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<210> 12

<211> 409

<212> DNA

<213> Homo sapiens

<400> 12

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cacgcgtgct tagccctcat agtaatagcc tctaccttc aggctgaaa accattgtgg 60
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tgagcgtatt tgctctaatt gggctgcagc tgttcattgg caacctgagg aataaatgta 180
tacaatggcc tcccaccaat gcttccttgg aggaacatag tatagaaaag aatataactg 240
tgaattataa tggtagactt ataaatgaaa ctgtctttga gtttgactgg aagtcataata 300
ttcaagattc aagtaagaat tattgttatg tacatttcct taaaaagtag aattggattg 360
tttgtaacac aaaggataaa tacttgaggg gctggatata ccattttac                                     409

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<210> 13
 <211> 266
 <212> DNA
 <213> Homo sapiens

<400> 13
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 cgactttcct ttttcaaaca ggatatcatt atttcttgga gggtttttta gatgcactac 180
 tatgtggaaa tagctctgat gcagggtaag tcaatattgt gtgcactctgt gtatattgta 240
 tgtacacaat acatatgtgt atcttt 266

<210> 14
 <211> 604
 <212> DNA
 <213> Homo sapiens

<400> 14
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 gaaatagatt agttacttat ttgtcaaact tttattttga aataccaaat ctttctgact 180
 aggcaatata atagcatagt atcagagtaa aaaggcagca gaacgacttg taatactttc 240
 ttttacccca cttgcagcca atgtccagag ggatatatgt gtgtgacagc tggtagaaat 300
 cccaattatg gctacacaag ctttgatacc ttcagttggg cttttttgtc cttgtttcga 360
 ctaatgactc aggacttctg ggaaaatctt tatcaactgg tgagaactaa agagccacac 420
 tctccattta agtaaaagta tacaagaaaa ccaattgagt tatgaaatta aaaccggatg 480
 ataatatagt agaaagagca gaacttgaca cgagacttga gttcctctat cctattgatt 540
 ataacacata ctgagcagag tgatgccaag gattgcaatt ctctccatt tcttcttggc 600
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<210> 15
 <211> 378
 <212> DNA
 <213> Homo sapiens

<400> 15
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 acatgatatt ttttgatttg gtcattttct tgggctcatt ctacctaata aatttgatcc 180
 tggctgtggt ggccatggcc tacgaggaac agaatcaggc caccttgga gaagcagaac 240
 agaaagaggc cgaatttcag cagatgattg aacagcttaa aaagcaacag gaggcagctc 300
 aggtgaagctg ccctgctcat ggcactgacc tttatcgtct gatgtactat atgagagaag 360
 tagtctagag cgtgtgat 378

<210> 16
 <211> 845
 <212> DNA
 <213> Homo sapiens

<400> 16
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 cataataaat gttaccatgg agcaaaactaa attatctcca aaagccttca ttaggtagaa 180
 agaaaaaaaa aatctcctct tatacttgca gagaatcttc tctgtgagat gatcttcagt 240
 cagttcaata ttttttttaa aagccatgca aatacttcag ccctttcaaa gaaagataca 300
 gtctcttcag gtgctatgtt aaaatcattt ctcttcaata tagcaggcag caacggcaac 360
 tgcctcagaa cattccagag agcccagtg agcaggcagg ctctcagaca gctcatctga 420
 agcctctaag ttgagttcca agagtgtctaa ggaaagaaga aatcggagga agaaaagaaa 480
 acagaaagag cagtctggtg ggaagagaa agatgaggat gaattccaaa aatctgaatc 540
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 tgaaaagagg tactcctccc cacaccaggt atggcactgc tgagtttact gatgcatggt 660
 tgaaaattaa aacatgggag agagggggag atttagaaaa tggactcagg aatttttatc 720
 aactgaatca accactggtg tgttatattt aaacccatcc cttcttcaca tagttatgca 780
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<210> 17
 <211> 965
 <212> DNA
 <213> Homo sapiens

<400> 17
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 taatcccaag ggctagaaac tttcttttat caaggttaatt taatttaatg tgaatgcaca 180
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 accttgagaa tgattcctgg ttggtcacgc tgtgaatgca cctgcatctt gtaatatctt 840
 tgatagacta accaactaaa acttaaaacc ttagcagtcg cctgcacaaa cctgaatgca 900
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 gattt 965

<210> 18
 <211> 641
 <212> DNA
 <213> Homo sapiens

<400> 18
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 tgtgtttcat gaaattcact gtgtcaccat ttggttggtt gcttgtcata ttgctcaaä 240
 taattgttta atgcattagc attttttttt acagggaaca accactgaaa ctgaaatgag 300
 aaagagaagg tcaagttctt tccacgtttc catggacttt ctagaagatc cttcccaaag 360
 gcaacgagca atgagtatag ccagcattct aacaaatata gtagaagggt ggtaacaaat 420
 tctattttcg tttcaattat tttcaccaaa cttatattgt ctcatctcaa acaaatatat 480
 ttgtgagttg ggaatagtgc attctaataa aaagacagtc taattcaaga gctgttattt 540
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<210> 19
 <211> 818
 <212> DNA
 <213> Homo sapiens

<400> 19
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 ataaccttgg gaggtttaga gtaaactgta atttttttta caagtacaaa aaagggtgtc 180
 tctgtaacaa aaatgtgttg attactgaaa ataagtttag tggatatgaa ataatgtgt 240
 gtgtataaag tawacctttt ggtgggtctt tttttttttt ttcttaatct agaacttgaa 300
 gaatccaggc agaaatgccc accctgttgg tataaatttt ccaacatatt cttaatctgg 360
 gactgttctc catattgggtt aaaagtgaat catgttgtca acctgggtgt gatggaccca 420
 tttgttgacc tggccatcac catctgtatt gtcttaataa ctcttttcat ggccatggag 480
 cactatccaa tgacggacca tttcaataat gtgcttacag taggaaactt ggtaagcata 540
 ttggaaggta aatgtgttta gtcttcaaat tttctgcttg aaaaactgtt tacatttaat 600
 tgtgtatagc agtctttcaa ccaccttca tgcttcctgg cccctgcaaa atcgcaatta 660
 tatttagctg gctatactct acttttttgc caaaaataat cacccttaat gtgctcaca 720
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 ttttcaggat ccagaagtag ctcatagatt aagaacat 818

<210> 20
 <211> 645
 <212> DNA
 <213> Homo sapiens

<400> 20
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aactacaaat tgccatacaa atttaagtta gtaatagaat cattgtggga aaatagcata 180
agcattatgt tctaagagca aatcttatgt catgtatgtt attatctggt ggaattagat 240
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<210> 21

<211> 829

<212> DNA

<213> Homo sapiens

<400> 21

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<211> 909

<212> DNA

<213> Homo sapiens

<400> 22

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<211> 516

<212> DNA

<213> Homo sapiens

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<210> 24

<211> 640

<212> DNA

<213> Homo sapiens

<400> 24

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<210> 25

<211> 607

<212> DNA

<213> Homo sapiens

<400> 25

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<210> 26

<211> 336

<212> DNA

<213> Homo sapiens

<400> 26

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<210> 27

<211> 677

<212> DNA

<213> Homo sapiens

<400> 27

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677.

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<211> 457

<212> DNA

<213> Homo sapiens

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<210> 29

<211> 379

<212> DNA

<213> Homo sapiens

<400> 29

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<211> 393

<212> DNA

<213> Homo sapiens

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<210> 31
<211> 539
<212> DNA
<213> Homo sapiens

<400> 31
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3403

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<211> 8349

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<213> Homo sapiens

<400> 33

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Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Asp Glu Asn
35 40 45

Gly Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Ser Leu Pro Phe
50 55 60

Ile Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Val Pro Leu Glu Asp
65 70 75 80

Leu Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys
85 90 95

Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu
100 105 110

Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His
115 120 125

Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val
130 135 140

Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr
145 150 155 160

Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala
165 170 175

Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn
180 185 190

Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val
195 200 205

Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala
210 215 220

Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala
225 230 235 240

Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val
245 250 255

Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly
 260 265 270
 Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe
 275 280 285
 Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly
 290 295 300
 Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile
 305 310 315 320
 Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu
 325 330 335
 Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile
 340 345 350
 Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp
 355 360 365
 Thr Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp
 370 375 380
 Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr
 385 390 395 400
 Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu
 405 410 415
 Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn
 420 425 430
 Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln
 435 440 445
 Met Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Ala Ala
 450 455 460
 Ala Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile
 465 470 475 480
 Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys
 485 490 495
 Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Lys Gln Lys Glu
 500 505 510

Gln Ser Gly Glu Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser
515 520 525

Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser
530 535 540

Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu
545 550 555 560

Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser
565 570 575

Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp
580 585 590

Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg
595 600 605

Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn
610 615 620

Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met
625 630 635 640

Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu
645 650 655

Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu
660 665 670

Gly Thr Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Ser Tyr
675 680 685

His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala
690 695 700

Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
705 710 715 720

Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys
725 730 735

Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val
740 745 750

Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
755 760 765

Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
 770 775 780

Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly
 785 790 795 800

Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr
 805 810 815

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser
 820 825 830

Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val
 835 840 845

Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp
 850 855 860

Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
 865 870 875 880

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
 885 890 895

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
 900 905 910

Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe
 915 920 925

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
 930 935 940

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
 945 950 955 960

Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn
 965 970 975

Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala
 980 985 990

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly
 995 1000 1005

Arg Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu Phe
 1010 1015 1020

Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu Ile Lys
 1025 1030 1035 1040
 Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile Ser Asn His
 1045 1050 1055
 Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu Lys Asp Gly Asn
 1060 1065 1070
 Gly Thr Thr Ser Gly Ile Gly Ser Ser Val Glu Lys Tyr Val Val Asp
 1075 1080 1085
 Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr
 1090 1095 1100
 Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu
 1105 1110 1115 1120
 Glu Phe Ser Ser Glu Ser Asp Met Glu Glu Ser Lys Glu Lys Leu Asn
 1125 1130 1135
 Ala Thr Ser Ser Ser Glu Gly Ser Thr Val Asp Ile Gly Ala Pro Ala
 1140 1145 1150
 Glu Gly Glu Gln Pro Glu Val Glu Pro Glu Glu Ser Leu Glu Pro Glu
 1155 1160 1165
 Ala Cys Phe Thr Glu Asp Cys Val Arg Lys Phe Lys Cys Cys Gln Ile
 1170 1175 1180
 Ser Ile Glu Glu Gly Lys Gly Lys Leu Trp Trp Asn Leu Arg Lys Thr
 1185 1190 1195 1200
 Cys Tyr Lys Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe
 1205 1210 1215
 Met Ile Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile
 1220 1225 1230
 Glu Gln Arg Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val
 1235 1240 1245
 Phe Thr Tyr Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr
 1250 1255 1260
 Gly Phe Gln Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu
 1265 1270 1275 1280

Ile Val Asp Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr
 1285 1290 1295
 Ser Glu Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg
 1300 1305 1310
 Pro Leu Arg Ala Leu Ser Arg Phe Glu Gly Met Arg Ala Val Val Asn
 1315 1320 1325
 Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys
 1330 1335 1340
 Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala
 1345 1350 1355 1360
 Gly Lys Phe Tyr His Cys Ile Asn Tyr Thr Thr Gly Glu Met Phe Asp
 1365 1370 1375
 Val Ser Val Val Asn Asn Tyr Ser Glu Cys Lys Ala Leu Ile Glu Ser
 1380 1385 1390
 Asn Gln Thr Ala Arg Trp Lys Asn Val Lys Val Asn Phe Asp Asn Val
 1395 1400 1405
 Gly Leu Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp
 1410 1415 1420
 Met Asp Ile Met Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln
 1425 1430 1435 1440
 Pro Lys Tyr Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe
 1445 1450 1455
 Ile Ile Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile
 1460 1465 1470
 Ile Asp Asn Phe Asn Gln Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile
 1475 1480 1485
 Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu
 1490 1495 1500
 Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe
 1505 1510 1515 1520
 Gln Gly Met Val Phe Asp Phe Val Thr Lys Gln Val Phe Asp Ile Ser
 1525 1530 1535

Ile Met Ile Leu Ile Cys Leu Asn Met Val Thr Met Met Val Glu Thr
 1540 1545 1550

Asp Asp Gln Ser Gln Glu Met Thr Asn Ile Leu Tyr Trp Ile Asn Leu
 1555 1560 1565

Val Phe Ile Val Leu Phe Thr Gly Glu Cys Val Leu Lys Leu Ile Ser
 1570 1575 1580

Leu Arg Tyr Tyr Tyr Phe Thr Ile Gly Trp Asn Ile Phe Asp Phe Val
 1585 1590 1595 1600

Val Val Ile Leu Ser Ile Val Gly Met Phe Leu Ala Glu Leu Ile Glu
 1605 1610 1615

Lys Tyr Phe Val Ser Pro Thr Leu Phe Arg Val Ile Arg Leu Ala Arg
 1620 1625 1630

Ile Gly Arg Ile Leu Arg Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr
 1635 1640 1645

Leu Leu Phe Ala Leu Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly
 1650 1655 1660

Leu Leu Leu Phe Leu Val Met Phe Ile Tyr Ala Ile Phe Gly Met Ser
 1665 1670 1675 1680

Asn Phe Ala Tyr Val Lys Arg Glu Val Gly Ile Asp Asp Met Phe Asn
 1685 1690 1695

Phe Glu Thr Phe Gly Asn Ser Met Ile Cys Leu Phe Gln Ile Thr Thr
 1700 1705 1710

Ser Ala Gly Trp Asp Gly Leu Leu Ala Pro Ile Leu Asn Ser Gly Pro
 1715 1720 1725

Pro Asp Cys Asp Pro Asp Lys Asp His Pro Gly Ser Ser Val Lys Gly
 1730 1735 1740

Asp Cys Gly Asn Pro Ser Val Gly Ile Phe Phe Phe Val Ser Tyr Ile
 1745 1750 1755 1760

Ile Ile Ser Phe Leu Val Val Val Asn Met Tyr Ile Ala Val Ile Leu
 1765 1770 1775

Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu
 1780 1785 1790

Asp Asp Phe Glu Met Phe Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp
 1795 1800 1805
 Ala Thr Gln Phe Ile Glu Phe Ala Lys Leu Ser Asp Phe Ala Asp Ala
 1810 1815 1820
 Leu Asp Pro Pro Leu Leu Ile Ala Lys Pro Asn Lys Val Gln Leu Ile
 1825 1830 1835 1840
 Ala Met Asp Leu Pro Met Val Ser Gly Asp Arg Ile His Cys Leu Asp
 1845 1850 1855
 Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly Glu Ser Gly Glu Met
 1860 1865 1870
 Asp Ala Leu Arg Ile Gln Met Glu Glu Arg Phe Met Ala Ser Asn Pro
 1875 1880 1885
 Ser Lys Val Ser Tyr Glu Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln
 1890 1895 1900
 Glu Glu Val Ser Ala Ile Ile Ile Gln Arg Ala Tyr Arg Arg Tyr Leu
 1905 1910 1915 1920
 Leu Lys Gln Lys Val Lys Lys Val Ser Ser Ile Tyr Lys Lys Asp Lys
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 Gly Lys Glu Cys Asp Gly Thr Pro Ile Lys Glu Asp Thr Leu Ile Asp
 1940 1945 1950
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 1955 1960 1965
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 Arg Glu Ser Lys Lys
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<213> Homo sapiens

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Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Asp Glu Asn
 35 40 45

Gly Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Ser Leu Pro Phe
 50 55 60

Ile Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Val Pro Leu Glu Asp
 65 70 75 80

Leu Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys
 85 90 95

Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu
 100 105 110

Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His
 115 120 125

Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val
 130 135 140

Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr
 145 150 155 160

Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala
 165 170 175

Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn
 180 185 190

Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val
 195 200 205

Asn Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala
 210 215 220

Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala
 225 230 235 240

Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val

245		250		255
Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly				
260		265		270
Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe				
275		280		285
Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly				
290		295		300
Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile				
305		310		315
Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu				
325		330		335
Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile				
340		345		350
Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp				
355		360		365
Thr Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp				
370		375		380
Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr				
385		390		395
Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu				
405		410		415
Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn				
420		425		430
Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln				
435		440		445
Met Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Ala Ala				
450		455		460
Ala Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile				
465		470		475
Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys				
485		490		495
Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Lys Gln Lys Glu				

500	505	510
Gln Ser Gly Glu Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser		
515	520	525
Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser		
530	535	540
Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu		
545	550	555
Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser		
565	570	575
Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp		
580	585	590
Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg		
595	600	605
Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn		
610	615	620
Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met		
625	630	635
Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu		
645	650	655
Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu		
660	665	670
Gly Thr Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Ser Tyr		
675	680	685
His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala		
690	695	700
Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu		
705	710	715
Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys		
725	730	735
Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val		
740	745	750
Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys		

755		760		765
Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr				
770		775		780
Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly				
785		790		800
Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr				
	805		810	815
Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser				
	820		825	830
Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val				
	835		840	845
Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp				
	850		855	860
Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala				
	865		870	875
Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala				
	885		890	895
Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys				
	900		905	910
Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe				
	915		920	925
Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile				
	930		935	940
Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu				
	945		950	955
Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn				
	965		970	975
Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala				
	980		985	990
Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly				
	995		1000	1005
Arg Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu Phe				

1010	1015	1020
Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu Ile Lys		
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Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile Ser Asn His		
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Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu Lys Asp Gly Asn		
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Gly Thr Thr Ser Gly Ile Gly Ser Ser Val Glu Lys Tyr Val Val Asp		
1075	1080	1085
Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr		
1090	1095	1100
Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu		
1105	1110	1115 1120
Glu Phe Ser Ser Glu Ser Asp Met Glu Glu Ser Lys Glu Lys Leu Asn		
1125	1130	1135
Ala Thr Ser Ser Ser Glu Gly Ser Thr Val Asp Ile Gly Ala Pro Ala		
1140	1145	1150
Glu Gly Glu Gln Pro Glu Val Glu Pro Glu Glu Ser Leu Glu Pro Glu		
1155	1160	1165
Ala Cys Phe Thr Glu Asp Cys Val Arg Lys Phe Lys Cys Cys Gln Ile		
1170	1175	1180
Ser Ile Glu Glu Gly Lys Gly Lys Leu Trp Trp Asn Leu Arg Lys Thr		
1185	1190	1195 1200
Cys Tyr Lys Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe		
1205	1210	1215
Met Ile Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile		
1220	1225	1230
Glu Gln Arg Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val		
1235	1240	1245
Phe Thr Tyr Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr		
1250	1255	1260
Gly Phe Gln Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu		

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Ile Val Asp Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr	1285	1290	1295
Ser Glu Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg	1300	1305	1310
Pro Leu Arg Ala Leu Ser Arg Phe Glu Gly Met Arg Ala Val Val Asn	1315	1320	1325
Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys	1330	1335	1340
Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala	1345	1350	1355
Gly Lys Phe Tyr His Cys Ile Asn Tyr Thr Thr Gly Glu Met Phe Asp	1365	1370	1375
Val Ser Val Val Asn Asn Tyr Ser Glu Cys Lys Ala Leu Ile Glu Ser	1380	1385	1390
Asn Gln Thr Ala Arg Trp Lys Asn Val Lys Val Asn Phe Asp Asn Val	1395	1400	1405
Gly Leu Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp	1410	1415	1420
Met Asp Ile Met Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln	1425	1430	1435
Pro Lys Tyr Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe	1445	1450	1455
Ile Ile Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile	1460	1465	1470
Ile Asp Asn Phe Asn Gln Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile	1475	1480	1485
Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu	1490	1495	1500
Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe	1505	1510	1515
Gln Gly Met Val Phe Asp Phe Val Thr Lys Gln Val Phe Asp Ile Ser			1520

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Asp Asp Gln Ser Gln Glu Met Thr Asn Ile Leu Tyr Trp Ile Asn Leu		
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Val Phe Ile Val Leu Phe Thr Gly Glu Cys Val Leu Lys Leu Ile Ser		
1570	1575	1580
Leu Arg Tyr Tyr Tyr Phe Thr Ile Gly Trp Asn Ile Phe Asp Phe Val		
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Lys Tyr Phe Val Ser Pro Thr Leu Phe Arg Val Ile Arg Leu Ala Arg		
1620	1625	1630
Ile Gly Arg Ile Leu Arg Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr		
1635	1640	1645
Leu Leu Phe Ala Leu Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly		
1650	1655	1660
Leu Leu Leu Phe Leu Val Met Phe Ile Tyr Ala Ile Phe Gly Met Ser		
1665	1670	1675 1680
Asn Phe Ala Tyr Val Lys Arg Glu Val Gly Ile Asp Asp Met Phe Asn		
1685	1690	1695
Phe Glu Thr Phe Gly Asn Ser Met Ile Cys Leu Phe Gln Ile Thr Thr		
1700	1705	1710
Ser Ala Gly Trp Asp Gly Leu Leu Ala Pro Ile Leu Asn Ser Gly Pro		
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Pro Asp Cys Asp Pro Asp Lys Asp His Pro Gly Ser Ser Val Lys Gly		
1730	1735	1740
Asp Cys Gly Asn Pro Ser Val Gly Ile Phe Phe Phe Val Ser Tyr Ile		
1745	1750	1755 1760
Ile Ile Ser Phe Leu Val Val Val Asn Met Tyr Ile Ala Val Ile Leu		
1765	1770	1775
Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu		

1780 1785 1790
 Asp Asp Phe Glu Met Phe Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp
 1795 1800 1805
 Ala Thr Gln Phe Ile Glu Phe Ala Lys Leu Ser Asp Phe Ala Asp Ala
 1810 1815 1820
 Leu Asp Pro Pro Leu Leu Ile Ala Lys Pro Asn Lys Val Gln Leu Ile
 1825 1830 1835 1840
 Ala Met Asp Leu Pro Met Val Ser Gly Asp Arg Ile His Cys Leu Asp
 1845 1850 1855
 Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly Glu Ser Gly Glu Met
 1860 1865 1870
 Asp Ala Leu Arg Ile Gln Met Glu Glu Arg Phe Met Ala Ser Asn Pro
 1875 1880 1885
 Ser Lys Val Ser Tyr Glu Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln
 1890 1895 1900
 Glu Glu Val Ser Ala Ile Ile Ile Gln Arg Ala Tyr Arg Arg Tyr Leu
 1905 1910 1915 1920
 Leu Lys Gln Lys Val Lys Lys Val Ser Ser Ile Tyr Lys Lys Asp Lys
 1925 1930 1935
 Gly Lys Glu Cys Asp Gly Thr Pro Ile Lys Glu Asp Thr Leu Ile Asp
 1940 1945 1950
 Lys Leu Asn Glu Asn Ser Thr Pro Glu Lys Thr Asp Met Thr Pro Ser
 1955 1960 1965
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 1970 1975 1980
 Lys Phe Glu Lys Asp Lys Ser Glu Lys Glu Asp Lys Gly Lys Asp Ile
 1985 1990 1995 2000
 Arg Glu Ser Lys Lys
 2005

<210> 37
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<213> Homo sapiens

<400> 37

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agcttatcaa tcccaaactc tgggggtaaa agattctaca ggggtaatgt tttattattc 480
ttattatgct tattctctgt gatgcttctc tacctttaca gtagtagaat ccttggggaa 540
atctgcagag ggaccacttt cattttgaag ctgctggctg catgttttag catgtctctt 600
ctattagaga atccaggcat ggcagtttcc tccccagtg tgcaaggacc atcttcatgc 660
ctatgtctgt cgctaggcat gaggtctctc aggaatgggt gaaaaaaatg agggatgttt 720
tgagggactc ataatactgg ggagggcagt ctgctagctg gtagctgaaa ggtcctgggt 780
tacttcaaca ttttttttaa ataaaactgt gcagtagttt ttgttatttt agggttccct 840
ctgttttatt tgggtgatgc tgcagaagtg aactgcataa cacatttcac tcttagaaat 900
gcattccata ta                                     912

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<210> 38

<211> 722

<212> DNA

<213> Homo sapiens

<400> 38

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ctcagtgcac gtaactgaca caatcacctc tatctaattg tcatgcttct tacctcctgt 60
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ggcacagtca gtgctggtac cgccaggacc tgacagcttc cgcttcttta ccagggaatc 180
ccttgctgct attgaacaac gcattgcaga agagaaagct aagagacca aacaggaacg 240
caaggatgag gatgatgaaa atggcccaaa gccaaacagt gacttgggaag cagsaaaatc 300
tcttccattt atttatggag acattcctcc agagatgggt tcagtgtccc tggaggatct 360
ggacccttac tatatcaata agaaagttag ttcttagtca agttgccttc actgcctatt 420
tactaattgg ttctgggcta gtcccaggga tgatggtgaa gaaggctggc ctccctccct 480
ctgtctaaag tatcactaag atgctggatg ggcctgaccg tgtaatggac caatgatcct 540
agaagtcttt tggaagcact catttgaacc tgcatttgtg agacaggcag agaactgggt 600
aggcatcctc cagcgcgggg attaaggaag gacaaaagcc tattcacctt cttgaataca 660
aatttatatg ttaaaccagt gttaaattgac cctgattccc taataatgtt gagaagcaaa 720
aa                                     722

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<210> 39

<211> 561

<212> DNA

<213> Homo sapiens

<400> 39

cctatggcat tgatcacaaa ttttcttaat aatcctcatg tcatttatca aatttaggaa 60...
agtttatagt gtcagaaaa aaaaagcatc tatcttcatg tcatatgatg gtaattatta 120
tggtatacac tattttacag ggcaatattt ataaataatg gttttacttt tctcttaaaa 180
tattcttaat atatatctta agttttgttt tatgtgttgt gttttctttt tcagacgttt 240
atagtattga ataaagggaa agcaatctct cgattcagtg ccaccctgc cctttacatt 300
ttaactccct tcaaccctat tagaaaatta gctattaaga ttttggtaga ttcatatcct 360
ttttcaaatc gtcacttaat atgattttct tctttgacca agttattgag ctacacattt 420
tccaaaatat ctgtggttg caatgttatg tgttctttct ttttctttcc ttttactcaa 480
tcgtagcat gttgcaaaat gagatcacag gtaagtgaat tactttcccc cgtcttctaa 540
gtgtttcttc tctacccaac t 561

<210> 40
<211> 510
<212> DNA
<213> Homo sapiens

<400> 40
acctaaatag cctcaaaaata gttgatggct tggcctgaag acaagatcta aatatgaggt 60
tgctgagtta tagaaatggc aaaaaaaagg gtcaataata gaataataag caacaaaata 120
atagtaagca ctaaagtttt aaacttcatg gtggtgaagg catggtagtg cataaaagta 180
agatttttcc attgaacttt gtcttccttg acgatattct actttattca atatgctcat 240
tatgtgcacg attcttacca actgtgtatt tatgaccatg agtaaccctc cagactggac 300
aaagaatgtg gagtaagtat aaatatTTTT caatatggac ctccctttat gtttcatatt 360
gtgcttttaa caccttgaga cctcctcaat ttctttaaca aatcatgcta gctactgtta 420
accagaccct gattcaaatt catttctgtc actaaatgtc ttctaggaca aagcttgtag 480
tgggctcact tagttgtgta aattactgca 510

<210> 41
<211> 370
<212> DNA
<213> Homo sapiens

<400> 41
taagatatgt acttgtaaata taaccactag atttttaatg tgagcttggc tattgtctct 60
caggtatacc tttacaggaa tttatacttt tgaatcactt attaaaatac ttgcaagggg 120
cttttgttta gaagatttca cattttttacg ggatccatgg aattggttg atttcacagt 180
cattactttt gcgtaagtat cttaatacat tttctatcct ggaagagtaa atcactgggtg 240
ggagcctata ctatatTTTt cttggtggct tgccttgaca gaccaagcat ttntcttagt 300
aatcatagtt ttcttccaat caaattatcc agtttgaga aattaggaac tatcatagta 360
aattacatgg 370

<210> 42
<211> 370
<212> DNA
<213> Homo sapiens

<400> 42

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caattagcac tgtaaagtaa taaagtttcc caaataacag agattatgat tgatgacaat 60
gccattttcc tcttaattgg gaaagctgat ggcgacactc atgaaattaa aaaggtcttg 120
atgaaagacc aangaagacg tagatttccc taaattctga ataactctga ttttaattcta 180
caggtatgta acagaatttg taaacctagg caatgtttca gctcttcgaa ctttcagagt 240
cttgagagct ttgaaaacta tttctgtaat tccaggtaag aagaaaatgg tataagggtgg 300
taggcccctt atatctccaa ctgtttcttg tgttctgtca ttgtgtttgt gtgtgaaccc 360
cctattacag                                     370

```

<210> 43

<211> 410

<212> DNA

<213> Homo sapiens

<400> 43

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gtaagaagaa aatggtataa ggtggtaggc cccttatatc tccaactggt tcttgtgttc 60
tgtcattgtg tttgtgtgtg aacccctat tacagatatg tgacagagtt tgtggacctg 120
ggcaatgtct cagcgttgag aacattcaga gttctccgag cattgaaaac aatttcagtc 180
attccagggtg agagctagggt taaacaccga ggctgacttt agctacagtg gtgctacaat 240
cacagctttt gtgcagaagc cttgttgcta gttgcatatt gcaaataaat atgtaaaaaa 300
gcaagaattg gtacatcatt ttttggtatg atttgattct ttgcttttta cccgttgctt 360
tctttaaaac tattctaaat cagcctttga gtttaacaag tgttgcatga 410

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<210> 44

<211> 1066

<212> DNA

<213> Homo sapiens

<400> 44

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aaagagtgtt tggaaataca catttggttc atttccattc acagttttct aatgaacata 60
caagttctgc tttcattcat tttcaccagc tagtaggctt ttcattgaaa tgttattcaa 120
tcacaaacat taaactaata ttgttggcat tctgcatgac atttttattt tccaggccaa 180
gctcatgata tttttgccgg taaaatagct gttgagtagt atatttaant tcccccttct 240
gattttgttt gtaggcctga agaccattgt gggggccctg atccagtcag tgaagaagct 300
ttctgatgtc atgatcttga ctgtgttctg tctaagcgtg tttgcgctaa taggattgca 360
gttggttcatt ggcaacctac gaaataaatg tttgcaatgg cctccagata attcttcctt 420
tgaaataaat atcacttctt tctttaacaa ttcattggat ggggaatggt ctactttcaa 480
taggacagtg agcatattta actgggatga atatattgag gataaaaagta agatatactc 540
tataaaccat taagttgttt agttctctaa atattaaata ttatatataa tggaaattat 600
ctcaatttag atgtgaatca agtgacttag actaatttaa gatgatttaa tacatataaa 660
agagatatca aaggatacct tattctattt ttsttatctg tccattgata tagtaaaagt 720
tctcatttga aaatgtgttg tcttatactc atgttgaaag taatttcata ttatgccata 780
ttaaaaaaagg tttatttggt agacattaat caggtttttc agtcatttta ataaataagt 840
cagtagtttg aactattcmg cgtattccac tgaaatgtcg ttaagaagac tgaggggaaa 900
taatttggcc ctatttggtt gatgcaacat atgtattgag tacatatgct atatctgaaa 960

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ctagagaaac catttatcaa gatgaaataa gaatttgtgt gctcctcaga aggttaagta 1020
 accctgattt agccattcac ttcattccata ttctaattag tccctt 1066

<210> 45
 <211> 385
 <212> DNA
 <213> Homo sapiens

<400> 45
 gttcaattat tgtgaaaaat cttcttttagc catatatatt tattagttta tccatctcat 60
 tatgattgaa aacattttgtg agctttgccca cctaaacagg gtggctgaag tgttttacag 120
 gattttaatg attcttttcta ttcctttctc tttaaataagg tcacttttat tttttacagg 180
 ggcaaaatga tgctctgctt tgtggcaaca gctcagatgc agggtaagtg tatgcttcct 240
 actgagtttc agtcacact gctccatcag tgtcaataac ctgccacctc ccactcatcc 300
 agtcccacca ctctcactc aaaaccctcc ataaattcta cttcacggtg actctcagaa 360
 tgaccaggat aagtgtagat tctca 385

<210> 46
 <211> 430
 <212> DNA
 <213> Homo sapiens

<400> 46
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 cattatataa atcagttcac ttagtgctga gttaagtact gggtaagggtg agagaaatcg 120
 gcttttttct agtgctgtga taaaacagac attggcatat attaaaacag gaaaaccaat 180
 tagcagactt gccgttattg actycctctc tttcctctaa cctaattaca gccagtgtcc 240
 tgaaggatac atctgtgtga aggctggtag aaaccccaac tatggctaca cgagctttga 300
 cacctttagt tgggcctttt tgccttatt tcgtctcatg actcaagact tctgggaaaa 360
 cctttatcaa ctggtgagaa cagataaaat catttttctg agaatcataa aacaccgaac 420
 tcaagagaat 430

<210> 47
 <211> 646
 <212> DNA
 <213> Homo sapiens

<400> 47
 tgctgtagaa tattttatta cttagagtgt aagtttgtaa catcctatat aaaatttatt 60
 aaaatctctc ttccattttg cagacactac gtgctgctgg gaaaacgtac atgatatttt 120
 ttgtgctggc cattttcttg ggctcattct atctaataaa tttgatcttg gctgtggtgg 180
 ccatggccta tgaggaacag aatcaggcca cattggaaga ggctgaacag aaggaagctg 240
 aatttcagca gatgctcgaa cagttgaaaa agcaacaaga agaagctcag gtatagttaa 300
 caagcatatg gtcctttgtt tttctgtatc taaattcttt aacctaaatg ttgaggtcag 360
 tggcaaggta gttgacatta gaaatagggtc atatgtgttt ggtaagtgtc aggagcctgt 420

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ttggttatta agaagttatt actttattgc aatgatctct gtcaatagtg tcaatagtaa 480.
tggcatcaaa aaatggataa ttataattgc tttactgaca tttttttctc ccttggtgact 540
ccttgaggaa attaatgatt aacaaaggcc tcatgtactc aaacttgcag agtagataaa 600
cctacatgct ctcagttgaa gtatttttctt aggggaagag gaattc 646

```

<210> 48

<211> 711

<212> DNA

<213> Homo sapiens

<400> 48

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tatgtatcat cttccatatt aatgcgcatt ttactctttg attggtctaa taacagtgtg 60
ctgtgttcta aaacacagaa taaaatggag aattgttttt caagattatc ttcattgatat 120
tgaagctcaa ttaagcagta acatgataat ttttttttaa gatnatatgc aacttcccac 180
atactttgct cctttctagg cggcagctgc agccgcattc gctgaatcaa gagacttcag 240
tggtgctggt gggataggag ttttttcaga gaggcttcca gtagcatcta agttgagctc 300
caaaagttaa aaagagctga aaaacagaag aaagaaaaag aaacagaaaag aacagtctgg 360
agaagaagag aaaaatgaca gagtcctaaa atcggaatct gaagacagca taagaagaaa 420
aggtttccgt ttttccttgg aaggaagtag gctgacatat gaaaagagat tttcttctcc 480
acaccaggta aaaatattaa attacatgaa ttgtgttctc ataaattttt taaaagaata 540
tgccagaatt taatggagag aaaaccgcct tccacctgga tggcacaatg ctttcagagt 600
agtgatgatt atcaagtgtt ttggctatca cttcagagaa tttgtgagtt ttgcaacttt 660
ttggaatccc aggaaggaaa ttttagatcc ctctgggttt ggaaaaattt g 711

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<210> 49

<211> 1026

<212> DNA

<213> Homo sapiens

<400> 49

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ttatggggac acttctgact atggtgaggt gtgggtaaag taggagaaaa gagagcagaa 60
gatggaaaat ggaggaagga gaaaaagcga gaggtaaata gaaaagggtga acctgtgata 120
aagtgccaaa atgccaccag cagtcattcag aggggtgctt tcttccacat gtccaatgac 180
ttatccttga gtaagtcaat gactatgaca caatgaatca aattctgttt ttcagaatgc 240
cagctcttaa ctctcttcat ctcatTTTTTg tttcttttct tgttattcat agtccttact 300
gagcatccgt ggctcccttt tctctccaag acgcaacagt agggcgagcc ttttcagctt 360
cagaggtcga gcaaaggaca ttggctctga gaatgacttt gctgatgatg agcacagcac 420
ctttgaggac aatgacagcc gaagagactc tctgttcgtg ccgcacagac atggagaacg 480
gcgccacagc aatgtcagcc aggccagccg tgcctccagg gtgctcccca tcttgcccat 540
gaatgggaag atgcatagcg ctgtggactg caatgggtgtg gtctccctgg tcgggggccc 600
ttctaccctc acatctgctg ggcagctcct accagagggtg aggccaaacy magattgcag 660
ctgatgtgaa gagagttgtg actggtgcag gcaggagtgy ttttccattt mcacatctaa 720
gaatttkttg agtttsttgc ccaaaggctg ggagtttgtt caatcaagct gttaactgtc 780
ttgtgaaact sttctattca gacttttycta caaagtaatt aaaaacctag gttggctgtc 840
agagaatata attagamgtm atcttttcatc ayyattacta tgggtatgaaa ctgcgcaaaa 900
agcaaagcaa caatttatca agcataatgt tygaytaata tagttaaatt aaatccaagg 960

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aaattaatgc tcacaaatta aataaatact taaggatttt gtgattgttg ttcattttaa 1020
aggaga 1026

<210> 50
<211> 601
<212> DNA
<213> Homo sapiens

<400> 50
ataggaaagc ccaccttgac aaaccaggg ctccccaaaa gctgaaaatc tgacagactt 60
taaacaaccc ccaaataatt atcattccaa caatatctta gtgagctttt tacatctgag 120
aaagcatggt gtatatcttag tttaaataaca cctggtgtag gaatgctttg ggctttgctg 180
ctttcaaaaa tagtggttat ttcactctgaa attctacttc tagggcacia ctactgaaac 240
agaaataaga aagagacggt ccagttctta tcatgtttcc atggatttat tggaagatcc 300
tacatcaagg caaagagcaa tgagtatagc cagtattttg accaacacca tggaaggat 360
gttaaaagtc ctgcgtcaca gttacttggt gctttcctaa tgatgaaaaa cacttcataa 420
atttcaataa aatacttctt gacttgatat tgtatcatta ttacacattt tactaaataa 480
cagtaaaatc cgtgcataac tcatggattc atatattcca cagatttttt ttttttatat 540
ttagcctgta gaaagctgct gcaaagttaa ggtatatattg aacaccactt tcataactta 600
a 601

<210> 51
<211> 645
<212> DNA
<213> Homo sapiens

<400> 51
gcttactagc ctttctgtac tgatcctttc tatgacagca aaccattgtt aaaattttcc 60
ctgttcctcc agcagattaa ccataatat cttttaacaa ctttagattt tttaaattcc 120
ttttaattta aaccaaatct gcttaataga aagtaagcag ttttcatgag gattctaact 180
ttttttcttc cagaacttga agaatccaga cagaaatgcc caccatgctg gtataaattt 240
gctaatatgt gtttgatttg ggactgttgt aaaccatggt taaagggtgaa acaccttgtc 300
aacctggttg taatggaccc atttggtgac ctggccatca ccatctgcat tgtcttaaat 360
acactcttca tggctatgga gcactatccc atgacggagc agttcagcag tgtactgtct 420
gttggaacc tggtaagcct cactgagagt ttctcttctt cttgaaagag ttataatttg 480
ccttagtgaa ttttacatat tgctctcaaa ttaaataatca actaattggc catgtatatc 540
ttgacatcaa atgttttagca tcccttttaa ataacaaaaa aatgttgcta ccatagtgca 600
aaagagtcaa agaatttatg tacaatttga tttagaattg aattt 645

<210> 52
<211> 485
<212> DNA
<213> Homo sapiens

<400> 52

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tggcccaaac caatttttaa atcaggaatt taatttwtat attggtggga gttaaattaa 60...
gttgctcaat aattattcgt gtttcaakas tatttgctca tataatgaac tacacttctc 120
atntaggtct tcacagggat cttcacagca gaaatgttcc tcaagataat tgccatggat 180
ccatattatt actttcaaga aggctggaat atttttgatg gttttattgt gagccttagt 240
ttaatggaac ttggtttggc aaatgtggaa ggattgtcag ttctccgatc attccggctg 300
gtaaattaaac tgggagtgtt cataaaatgt actttrtaat taattagtct tcattctcat 360
ctagtaaaaa tggcaagatt tcccatcatt ataataatatt tgaatacctt ctaaaacaga 420
ttggattgcc ataccaccaa atggtagttt cttcttcac atagctttaa taaagttcac 480
ttaaa 485

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<210> 53

<211> 602

<212> DNA

<213> Homo sapiens

<400> 53

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acagatttcc tctgtgtcc atgtgactaa cccattgtgc acatgtaccc taaaaattag 60
tatataataa taaaataaaa taaaaataaa aataaaaaaa taaaaataaa ataaaattgc 120
agattttttt agaaatgcag agattaacac tgttcttgct tttatttcca gctccgagtt 180
ttcaagttgg caaaatcttg gccaaactcta aatatgctaa ttaagatcat tggcaattct 240
gtgggggctc taggaaacct caccttggtt ttggccatca tctgttcat ttttgctgtg 300
gtcggcatgc agctcttttg taagagctac aaagaatgtg tctgcaagat ttccaatgat 360
tgtgaactcc cacgctggca catgcatgac tttttccact ccttcctgat cgtgttccgc 420
gtgctgtgtg gagagtggat agagaccatg tgggactgta tggaggtcgc tggccaaacc 480
atgtgcctta ctgtcttcat gatggtcatg gtgattggaa atctagtggg atgtagcaaa 540
aacattttcc tcattttcat taaaaataat gtaatcatta aaaagtgttc aactgaagaa 600
ta 602

```

<210> 54

<211> 803

<212> DNA

<213> Homo sapiens

<400> 54

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gtttcattta gcaatgattt cagtattttc tgcaatgact aataagcaaa tagtgataat 60
agtattattt tatattgacc aagcattttt atttcattca ctttttttca gaatagtgtt 120
tcatgaatta gcagaaatgc atgttagaat aaaataaggt gtcaagaaca atcttagaaa 180
actaatgatg gaaagcaatt gaagcaatag aatgttttga tcacctgttt ttctgctgt 240
gtttcaggtt ctgaacctct tcttgccctt gcttttgagt tcttcagtt ctgacaatct 300
tgctgccact gatgatgata acgaaatgaa taatctccag attgctgtgg gaaggatgca 360
gaaaggaatc gattttgtta aaagaaaaat acgtgaattt attcagaaag cttttgttag 420
gaagcagaaa gcttttagatg aaattaaacc gcttgaagat ctaaataata aaaaagacag 480
ctgtatttcc aaccatacca ccatagaaat aggcaagac ctcaattatc tcaaagacgg 540
aaatggaact actagtggca taggcagcag ttagaaaaa tatgtcgtgg atgaaagtga 600
ttacatgtca ttataaaaca accctagcct cactgtgaca gtaccaattg ctgttgaga 660
atctgacttt gaaaatttaa atactgaaga attcagcagc gagtcagata tggaggaaa 720

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caaagaggta aaatgttaaa taaggagata ttttggtgta tataatctgt gttaaataac 780
 aggtgtttta tgcgtgtctc tgt 803

<210> 55
 <211> 615
 <212> DNA
 <213> Homo sapiens

<400> 55
 atctctatac taggctcaaa cagaagttat ttccgttggt agcaccatat ttttaaaaga 60
 aaaaaaata ctatggtggt gtatctaata ttgtgacccc tgacctttac caaagcggat 120
 tggcattatg ttttaagttct taattacaga tcaagaaaaa tgcatacaga agatgggggg 180
 gggcacacct aattaatttt tatatttaga ttaaagaaaa taattaaatg tgtttttttg 240
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 tggagctccc gccgagggag aacagcctga ggttgaacct gaggaatccc ttgaacctga 360
 agcctgtttt acagaagnnn nnnnnnaagc aaaacaataa catatgtggt cttgagtatc 420
 ctcttttcta cccatttttt cctattttatt taaatgtctg tttatttgtc taccatctag 480
 ttcatctatc tatctgtatc tatctatcta tctatctatc tagtaatcat ctatacctat 540
 ccaacaactg tacattttatt tgtttttttt ttttgcattt gctgtttgaa aaaaaatgca 600
 acgttttaaa ggcaa 615

<210> 56
 <211> 400
 <212> DNA
 <213> Homo sapiens

<400> 56
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 gtaataatgt aaatgaatct cccaccaaca caaatatacc taatcaaaga gtaatttttt 120
 gtcttcattt ttttcccaca tatttttagac tgtgtacgga agttcaagtg ttgtcagata 180
 agcatagaag aaggcaaagg gaaactctgg tggaaattga ggaaaacatg ctataagata 240
 gtggagcaca attggttcga aaccttcatt gtcttcattga ttctgctgag cagtggggct 300
 ctggtaggtg atgcatgac cactccttca cctttcatct gaaatctttt ccctttccct 360
 tcaatcaact catattaccc acttttaaat taagggtgtt 400

<210> 57
 <211> 560
 <212> DNA
 <213> Homo sapiens

<400> 57
 aaattactga aacccttggt tgactgaaat gccagtcag cagtcattta tgatcagata 60
 atgataaagt aaaattcagc catgggaaac attaaacctt ccagccttag gcacctgata 120
 agagcttgca tcgtttcctt ttttaagaaa tcatcaatta gagactgttt ctgatcataa 180
 aatttaatat aattttttga cttacaggcc ttgaagata tatacattga gcagcgaaaa 240

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accattaaga ccatgttaga atatgctgac aaggttttca cttacatatt cattctggaa 300.
atgctgctaa agtgggttgc atatggtttt caagtgtatt ttaccaatgc ctgggtgctgg 360
ctagacttcc tgattgttga tgtgagtatg ctgcactttg ctgctttatt cattggcata 420
tatgtaatag ttctagcaat ggtgcctgac acagtgtagg cactcagtaa cactgtatca 480
gcccaaatat aaattatgtt tctcatttca cagtgaagagg atgcctcaaa acatttttta 540
ccaatttaaa tacatatata 560

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<210> 58

<211> 480

<212> DNA

<213> Homo sapiens

<400> 58

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aaattcttag gcctttcccc aaacttacta agtcagactc tgctattggt gtttttaaca 60
agacccttgg gtgattttga aactcatgaa agttcgagaa ttactgattc attgcataga 120
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<210> 59

<211> 640

<212> DNA

<213> Homo sapiens

<400> 59

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<210> 60

<211> 480

<212> DNA

<213> Homo sapiens

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<210> 61

<211> 366

<212> DNA

<213> Homo sapiens

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<210> 62

<211> 560

<212> DNA

<213> Homo sapiens

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<211> 650

<212> DNA

<213> Homo sapiens

<400> 63

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<211> 3700

<212> DNA

<213> Homo sapiens

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 Leu Ile Trp Asp Cys Cys Asp Ala Trp Leu Lys Val Lys His Leu Val
 690 695 700
 Asn Leu Ile Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
 705 710 715 720
 Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
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 Glu Gln Phe Ser Ser Val Leu Thr Val Gly Asn Leu Val Phe Thr Gly
 740 745 750
 Ile Phe Thr Ala Glu Met Val Leu Lys Ile Ile Ala Met Asp Pro Tyr
 755 760 765
 Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Ile Ile Val Ser
 770 775 780
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 785 790 795 800
 Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp
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 Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
 820 825 830
 Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
 835 840 845
 Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
 850 855 860
 Lys Ile Asn Asp Asp Cys Thr Leu Pro Arg Trp His Met Asn Asp Phe
 865 870 875 880

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
885 890 895

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
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Ile Val Phe Met Leu Val Met Val Ile Gly Asn Leu Val Val Leu Asn
915 920 925

Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala
930 935 940

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly
945 950 955 960

Arg Met Gln Lys Gly Ile Asp Tyr Val Lys Asn Lys Met Arg Glu Cys
965 970 975

Phe Gln Lys Ala Phe Phe Arg Lys Pro Lys Val Ile Glu Ile His Glu
980 985 990

Gly Asn Lys Ile Asp Ser Cys Met Ser Asn Asn Thr Gly Ile Glu Ile
995 1000 1005

Ser Lys Glu Leu Asn Tyr Leu Arg Asp Gly Asn Gly Thr Thr Ser Gly
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Val Gly Thr Gly Ser Ser Val Glu Lys Tyr Val Ile Asp Glu Asn Asp
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Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr Val Pro Ile
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Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu Glu Phe Ser
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Ser Glu Ser Glu Leu Glu Glu Ser Lys Glu Lys Leu Asn Ala Thr Ser
1075 1080 1085

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Gln Ala Glu Thr Glu Pro Glu Glu Asp Leu Lys Pro Glu Ala Cys Phe
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Glu Gly Lys Gly Lys Ile Trp Trp Asn Leu Arg Lys Thr Cys Tyr Ser
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 Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Ala Gly Tyr Leu Ala
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Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe
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Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln
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Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu Gln
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Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys Pro Gln
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Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe Gln Gly Met Val Phe Asp
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Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met Ile Leu Ile Cys
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Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Gly Lys Tyr
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Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile
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Val Gly Met Phe Leu Ala Glu Met Ile Glu Lys Tyr Phe Val Ser Pro
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Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg
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Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met
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Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe Leu Val
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Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala Tyr Val Lys
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Lys Glu Ala Gly Ile Asp Asp Met Phe Asn Phe Glu Thr Phe Gly Asn
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Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp Gly
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Leu Leu Ala Pro Ile Leu Asn Ser Ala Pro Pro Asp Cys Asp Pro Asp
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Thr Ile His Pro Gly Ser Ser Val Lys Gly Asp Cys Gly Asn Pro Ser
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Val Gly Ile Phe Phe Phe Val Ser Tyr Ile Ile Ile Ser Phe Leu Val
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Val Val Asn Ser Tyr Ile Ala Val Ile Leu Glu Asn Phe Ser Val Ala
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Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Ile Glu
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Phe Ser Lys Leu Ser Asp Phe Ala Ala Ala Leu Asp Pro Pro Leu Leu
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Ile Ala Lys Pro Asn Lys Val Gln Leu Ile Ala Met Asp Leu Pro Met
 1780 1785 1790

Val Ser Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr
 1795 1800 1805

Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln
 1810 1815 1820

Met Glu Asp Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Glu
 1825 1830 1835 1840

Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Ala
 1845 1850 1855

Ile Ile Gln Arg Asn Phe Arg Cys Tyr Leu Leu Lys Gln Arg Leu Lys
 1860 1865 1870

Asn Ile Ser Ser Asn Tyr Asn Lys Glu Ala Ile Lys Gly Arg Ile Asp
 1875 1880 1885

Leu Pro Ile Lys Gln Asp Met Ile Ile Asp Lys Leu Asn Gly Asn Ser
 1890 1895 1900

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<212> PRT

<213> Homo sapiens

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Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile
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Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu
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Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Met Asn Lys Gly
 85 90 95

Lys Ala Ile Ser Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr
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Pro Leu Asn Pro Val Arg Lys Ile Ala Xaa Lys Ile Leu Val His Ser
 115 120 125

Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe
 130 135 140

Met Thr Leu Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr
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Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp
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Leu Asp Phe Ser Val Ile Val Met Ala Tyr Val Thr Glu Phe Val Ser
 195 200 205

Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu
 210 215 220

Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu
 225 230 235 240

Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe
 245 250 255

Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn
 260 265 270

Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Ser Asp Ser Ala Phe Glu
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Thr Asn Thr Thr Ser Tyr Phe Asn Gly Thr Met Asp Ser Asn Gly Thr
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Phe Val Asn Val Thr Met Ser Thr Phe Asn Trp Lys Asp Tyr Ile Gly
 305 310 315 320

Asp Asp Ser His Phe Tyr Val Leu Asp Gly Gln Lys Asp Pro Leu Leu
 325 330 335

Cys Gly Asn Gly Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile Cys
 340 345 350

Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr
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Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Tyr
 370 375 380

Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr
 385 390 395 400

Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Val
 405 410 415

Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Gly Gln Asn Gln
 420 425 430

Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met
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Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Val Ala Ala
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485 490 495

Lys Glu Trp Arg Asn Arg Arg Lys Lys Arg Arg Gln Arg Glu His Leu
500 505 510

Glu Gly Asn Asn Lys Gly Glu Arg Asp Ser Phe Pro Lys Ser Glu Ser
515 520 525

Glu Asp Ser Val Lys Arg Ser Ser Phe Leu Phe Ser Met Asp Gly Asn
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Arg Leu Thr Ser Asp Lys Lys Phe Cys Ser Pro His Gln Ser Leu Leu
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Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Lys Thr Ser
565 570 575

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595 600 605

Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg Asn Ser Asn
610 615 620

Gly Thr Thr Thr Glu Thr Glu Val Arg Lys Arg Arg Leu Ser Ser Tyr
625 630 635 640

Gln Ile Ser Met Glu Met Leu Glu Asp Ser Ser Gly Arg Gln Arg Ala
645 650 655

Val Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
660 665 670

Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Arg Phe Ala Asn Val Phe
675 680 685

Leu Ile Trp Asp Cys Cys Asp Ala Trp Leu Lys Val Lys His Leu Val
 690 695 700

Asn Leu Ile Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
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Glu Gln Phe Ser Ser Val Leu Thr Val Gly Asn Leu Val Phe Thr Gly
 740 745 750

Ile Phe Thr Ala Glu Met Val Leu Lys Ile Ile Ala Met Asp Pro Tyr
 755 760 765

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Ile Ile Val Ser
 770 775 780

Leu Ser Leu Met Glu Leu Gly Leu Ser Asn Val Glu Gly Leu Ser Val
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Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
 835 840 845

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
 850 855 860

Lys Ile Asn Asp Asp Cys Thr Leu Pro Arg Trp His Met Asn Asp Phe
 865 870 875 880

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
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 1265 1270 1275 1280
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 1285 1290 1295
 Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala Gly Lys Phe
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 Tyr His Cys Val Asn Met Thr Thr Gly Asn Met Phe Asp Ile Ser Asp
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 Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Ala Gly Tyr Leu Ala
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 Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu Gln
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 Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys Pro Gln
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Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe Gln Gly Met Val Phe Asp
 1460 1465 1470

Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met Ile Leu Ile Cys
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Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Gly Lys Tyr
 1490 1495 1500

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Thr Gly Glu Phe Val Leu Lys Leu Val Ser Leu Arg His Tyr Tyr Phe
 1525 1530 1535

Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile
 1540 1545 1550

Val Gly Met Phe Leu Ala Glu Met Ile Glu Lys Tyr Phe Val Ser Pro
 1555 1560 1565

Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg
 1570 1575 1580

Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met
 1585 1590 1595 1600

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 1635 1640 1645

Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp Gly
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Leu Leu Ala Pro Ile Leu Asn Ser Ala Pro Pro Asp Cys Asp Pro Asp
 1665 1670 1675 1680

Thr Ile His Pro Gly Ser Ser Val Lys Gly Asp Cys Gly Asn Pro Ser
 1685 1690 1695

Val Gly Ile Phe Phe Phe Val Ser Tyr Ile Ile Ile Ser Phe Leu Val
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 1730 1735 1740

Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Ile Glu
 1745 1750 1755 1760

Phe Ser Lys Leu Ser Asp Phe Ala Ala Ala Leu Asp Pro Pro Leu Leu
 1765 1770 1775

Ile Ala Lys Pro Asn Lys Val Gln Leu Ile Ala Met Asp Leu Pro Met
 1780 1785 1790

Val Ser Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr
 1795 1800 1805

Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln
 1810 1815 1820

Met Glu Asp Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Glu
 1825 1830 1835 1840

Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Ala
 1845 1850 1855

Ile Ile Gln Arg Asn Phe Arg Cys Tyr Leu Leu Lys Gln Arg Leu Lys
 1860 1865 1870

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 1875 1880 1885

Leu Pro Ile Lys Gln Asp Met Ile Ile Asp Lys Leu Asn Gly Asn Ser
 1890 1895 1900

Thr Pro Glu Lys Thr Asp Gly Ser Ser Ser Thr Thr Ser Pro Pro Ser
 1905 1910 1915 1920

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<211> 1380

<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<400> 71

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<213> Homo sapiens

<400> 72

acaaagtatt gaaaaggcgg ggggcaggat gcagaataat taagcaattt tattgacaaa 60
ctthactggc attactcttt tgctgaaagt atactatatt ttggcttaca gtgtcaaac 120
agaatttttt aaatgctttt aaaaaatgga caaaattata gatattcttg agtttaaata 180
taatgtttat atattatata tactgtacat ttagaatgg cttaatcaaa ctaattaaca 240
ttaagtacag acttttgata gatttatgaa cttggcttat tgagaatgag gttgaatgat 300
gatgttttca agttcaaagtg ttagtgagc tactaaaagc atgacttaat gtttatagct 360
ttaaaaagtt actaaagaat gacatttttg ttgatgttct tatgcccatt cgcttgcttt 420
cctaactctt gtgcaatttt tctttttatt gcaggtaatt cgtatgcaag aagctacacg 480
taattaaatg tgcaggatga aaagatggca caggcactgt tggtagcccc aggacctgaa 540
agcttccgcc tttttactag agaattctct gctgctatcg aaaaacgtgc tgcagaagag 600
aaagccaaga agcccaaaaa ggaacaagat aatgatgatg agaacaacc aaagccaaat 660
agtgacttgg aagctggaaa gaaccttcca tttatttatg gagacattcc tccagagatg 720
gtgtcagagc cctggagga cctggatccc tactatatca ataagaaagt gagtattgat 780
tttagacttc taataaatct ttaatgaaac tcttaactgt aatatacttt tctgggcttt 840
atatacagca tcacaatttt tcttctgtta aagattttat aatactcttc actgtcactt 900
atttttatca caatataata aaacaaacat ttataagaaa tgaagtcaag agttgggttac 960
agtcaggaaa tatgaataga tgaatgattt ctacaatttc acagtataa ttcagatagt 1020

caaaa

1025

<210> 73

<211> 433

<212> DNA

<213> Homo sapiens

<400> 73

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tgtaacyata tgtaatttta aacatctaac atgtttgtag ttatgatata tcaactgggt 60
taaacaaacc agtttgaaca aacaaattcy attttttaaa aaggtcctca tgtatgtaag 120
ctccttaaat aagcccatgt ctaatttagt aattttactc gtattttctg tttcagactt 180
ttatagtaat gaataaagga aaggcaattt cccgattcag tgccacctct gccttgata 240
ttttaactcc actaaaccct gttaggaaaa ttgctabsaa gattttggta cattcatatc 300
cttttaatgt gaattgccta aatgctattt ctaacagttg attttaaga aaatgtcagt 360
tatattttca agtatctgta aaatttcttt gagattaatg gtaacattgt tagtttaatt 420
catttatttg cat 433

```

<210> 74

<211> 450

<212> DNA

<213> Homo sapiens

<400> 74

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gagtgcacca aggccatatc acaggctttg aagtttctta ttattttatc attgttttaa 60
aacaaataat attaatttca cagtttttgc atcgataaac ttttttggtg gttttggatc 120
atttataaat ggccatggta acctactaac atttattcct taactataat ctactttatt 180
cagcatgctt atcatgtgca ctattttgac caactgtgta tttatgacct tgagcaaccc 240
tcctgactgg acaaagaatg tagagtaagt aggaataact tctgggaatg agaaatgcac 300
actcaaattc tctagcaatc tccttggtgg tatagcctga cttatggttt ccacttctgt 360
ctaagaaaag ttattttcat aatatgcagc cggttaaggga ggtctttcgg gggagctatt 420
cttctacgag gtaagtattt tcccacaaaa 450

```

<210> 75

<211> 701

<212> DNA

<213> Homo sapiens

<400> 75

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aaaatttacc atttgyggct ttccattaca tttctatcag ataactctgc gctagtaggt 60
caaaactagat gattatccat agatacatg aaactattat tctaaaaccc aaatagttta 120
accagattag attcctaaag aatatatttt ctcttcagtt taactctttg ctcaggcttg 180
taaaactaac taaatgaata gattatttgg taaatagaag taaggaacaa tattttaatg 240
aattgaaaaa ccacaaaagg ataggatttg ctatgattga aaacatttat ttttaacagtt 300
caagcaaaat tgtaattttt ggcttggatg tttttcctag gtacacattc actggaatct 360
atacctttga gtcacttata aaaatcttgg caagagggtt ttgcttagaa gattttacgt 420

```

```

ttcttcgtga tccatggaac tggctggatt tcagtgtcat tgtgatggcg tgagtaactt 480.
tgaaaatttg ataagcgcaa aggagtgaag atagtcatag tacaaacaag gtctttgtgt 540
catatattaa atgtagagct ttcttgtagg tcaagttaac tatatgggtt gtgtattttc 600
agaatacata ttagaataca tattgcaatg taaatatatc cagtaaatag tcaataaatg 660
gggttatctt catgtcatat agtctttctc ttcacaaaa t 701

```

<210> 76

<211> 286

<212> DNA

<213> Homo sapiens

<400> 76

```

atttggttaaa ctcacagggc tctatgtgcc aaaccagca ttaagtcctt atttagtata 60
aactttgccaa aaactatcag taactctgat ttaattctgc aggtatgtaa cagaatttgt 120
aagcctaggc aatgtttcag cccttcgaac ttccagagtc ttgagagctc tgaaaactat 180
ttctgtaatc ccaggtaaga agaaactggg gtaaggtagt aggccctta tatctccaac 240
ttttcttggtg tgttattgtg ttgtgtgtg aactcccta ttacag 286

```

<210> 77

<211> 515

<212> DNA

<213> Homo sapiens

<400> 77

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gtaagaagaa actggtgtaa gtagtaggc cccttatatc tccaaacttt cttgtgtgtt 60
attgtgtttg tgtgtgaact cccctattac agatatgtga cagagtttgt ggacctgggc 120
aatgtctcag cgttgagaac attcagagtt ctccgagcac tgaaaacaat ttcagtcatt 180
ccaggtgaga gctagggtta acaccgaggt tgactttaat tattgagttt gaaatcaatt 240
tatatgactt acagcattag cttgttgct tattattaca gttcatcccg gtaataatg 300
ccaaatgatg tttcaatgtc agtttagct ctaaaatttt ataaattaca tgcgtattta 360
taaagtcagc ctttgagttt aacagaaaat tgcagagac atcttcaaaa aatgctaatt 420
tgggcctctt gcgctctctc tctctctttt tcaactaccat ggctttacta acagatttgg 480
attttaccat tcgctgcaga ttagattcaa aaatg 515

```

<210> 78

<211> 564

<212> DNA

<213> Homo sapiens

<400> 78

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aaacttcctg actagatatt taaaccttca tattgaattt ccagcaagca cactgttcat 60
gtgtaaaatc tgctgttcat ctatttccca aatcatcagg ctatccatac agctttgggtg 120
tctaaatagt caagcaatca tttatggggg aaagagaatg tgtgtgacta ttaagaaatc 180
atgatttctg gcaactcttc tcaggtaacc tatagttctc tctctgcagg tttaaagacc 240
attgtggggg ccctgatcca gtcggtaaag aagctttctg atgtgatgat cctgactgtg 300

```

ttctgtctga gcgtgtttgc tctcattggg ctgcagctgt tcatgggcaa tctgaggaat 360.
 aaatgtttgc agtggccccc aagcgattct gcttttgaaa ccaacaccac ttcctacttt 420
 aatggcaciaa tggattcaaa tgggacattt gttaatgtaa caatgagcac atttaactgg 480
 aaggataaca ttggagatga cagtaagaag tattacatta tgtaaacctt agtggtgctg 540
 aatgaatttt caactataaa tagt 564

<210> 79

<211> 497

<212> DNA

<213> Homo sapiens

<400> 79

tgagactgtg ggtgtacagc cacctttgta aataactgaa atagtccaac tctgatttat 60
 tactaatact aatgtgaata ggattaatat gaaataaaat gggttttttt ttgtattaac 120
 aggtcacttt tatgttttgg atgggcaaaa agacccttta ctctgtggaa atggttcaga 180
 tgcagggtaa gaaacataat atatatTTTT aagatataga actctttgcg aaaaaaaaaa 240
 gtaggtagga aaacaactac atgggtatat gtgtagcctt accatgtatg caataaagag 300
 cagtgtgct cccctaggaa gtgccttgct tgccttaccg gattgccact ggtcctaaac 360
 tcacagcaat taaaaattat ccccttggtg agacctttcc ccaaaatttc acagttaaga 420
 tgttcttaaa ttgatgtctc aatgtgtgaa ggcccagagt ctgtctttgc tgtacatcta 480
 tcagagctgt taggaaa 497

<210> 80

<211> 501

<212> DNA

<213> Homo sapiens

<400> 80

aaagagtaaa aatatggtaa ggtcagagcc aaaagtgtgt ggttgctagc tttctgccat 60
 tctaaatgtc trwaaawatt tatttgcac taaattttct atcggctctc ctagtgaatt 120
 tcatctgata agtttcacgg tgggcaatca cctaaagtgt tctggaaatt aaagcaagat 180
 aattcgtcac agatagcagc tttgggtttt gaaaattcct ataagtcaaa taaattgaaa 240
 ttgctgtaat ttctaaactg accctacctc catttctctc tcttatagcc agtgtccaga 300
 aggatacatc tgtgtgaagg ctggtcgaaa cccaactat ggctacacaa gctttgacac 360
 cttagctgg gctttcctgt ctctatttctg actcatgact caagactact gggaaaatct 420
 ttaccagttg gtaaggtcca aatgagcatg cataacattt atttttatag acatgtatga 480
 aatgaaaagc ataggctgag t 501

<210> 81

<211> 432

<212> DNA

<213> Homo sapiens

<400> 81

agctaattag tctactgact atctaactgt ggtaatcaga tatttatttg gggacattat 60

```

actaaaatac tgatggaatt atccccatt tcccctagac attacgtgct gctgggaaaa 120.
catacatgat attttttgtc ctgggtcattt tcttgggctc attttatttg gtgaatttga 180
tcttggtgt ggtggccatg gcctatgagg ggcagaatca ggccaccttg gaagaagcag 240
aacaaaaaga ggccgaattt cagcagatgc tcgaacagct taaaaagcaa caggaagaag 300
ctcagggtact gagtataaaa mgcaaagatt tatcattatt attmttagtt tctaagtaga 360
aatagtgtta tactatagag ggtagattgg aactgctttt tcattttata tatmggcatt 420
gtcattagac ac 432

```

<210> 82

<211> 489

<212> DNA

<213> Homo sapiens

<400> 82

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tgcaaactgt tttcaaagct ctgtgttcta aatagtgcct ggctttgttt tatgacaggc 60
agttgcggca gcatcagctg cttcaagaga tttcagtggg ataggtgggt taggagagct 120
gttggaaggt tcttcagaag catcaaagtt gagttccaaa agtgctaaag aatggaggaa 180
ccgaaggaag aaaagaagac agagagagca ccttgaagga aacaacaaag gagagagaga 240
cagctttccc aaatccgaat ctgaagacag cgtcaaaaga agcagcttcc ttttctccat 300
ggatggaaac agactgacca gtgacaaaaa attctgctcc cctcatcagg tatgattttc 360
tactaagtgc tctggtttct ttgtcattgc tattgctttt tagtttttgt attttgtttt 420
ggtacacttt tgtactatct gtacttcagt tgagggacag ggaactaaca tttaatatag 480
ttgtttaaa 489

```

<210> 83

<211> 653

<212> DNA

<213> Homo sapiens

<400> 83

```

gtgaagacta aatgaagtgg ttgtatactt agtaaattgc aaatcagtat tgtagtcag 60
aaaaacactc tttgtactta aatttgcttt aataaaaaata tcaaaatata tgtgtcctct 120
ataaatttga ttatccatgt ttaagggcaa gagtatacta actccaaaga aaacagatcc 180
tttaatatata atatttatta aataattgag ttcttccct acccccatcc cattcctttc 240
ctttttgctt tctctgcagt ctctcttgag tatccgtggc tccctgtttt cccaagacg 300
caatagcaaa acaagcattt tcagtttcag aggtcgggca aaggatgttg gatctgaaaa 360
tgactttgct gatgatgaac acagcacatt tgaagacagc gaaagcagga gagactcact 420
gtttgtgccg cacagacatg gagagcgacg caacagtaac gttagtcagg ccagtatgtc 480
atccaggatg gtgccagggc ttccagcaaa tggggaagat gcacagcact gtggattgca 540
atgggtgtgg ttccttggtg ggtggacctt cagctctaac gtcacctact gggcaacttc 600
cccagagggtg ataatatagatg acctagctgc tactgacatt attcaccaat ttg 653

```

<210> 84

<211> 566

<212> DNA

<213> Homo sapiens

<400> 84

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gaattctctt aaaggtacta cctgtgatac tttttttaaa aaaaaactgt ttataactta 60
gcaataattc aatattttat tcttgaaatt cttacctgga aaattgcatg tagcatgatt 120
tgcaaagaaa tgctatgtgg tgttgatta cttattggga agagtgggtt gagccatcag 180
tatttggttt gcagggcacc accactgaaa cggaagtcag aaagagaagg ttaagctctt 240
accagatttc aatggagatg ctggaggatt cctctggaag gcaaagagcc gtgagcatag 300
ccagcattct gaccaacaca atggaaggta agagcaggtc atggaacagc caactttctg 360
tgattatgtg ctttgtgaac tattccttct tttcatagaa ttactgaagt ctgttaccda 420
gatcgaacta tatattagac ctaagaatgt gatatatggt gtacattatc acattgntta 480
caaaactaat attggcctta ttctttttga cttgggtcct taccttactt gcagagtgat 540
atttcaacac ttgatattat atcaat 566

```

<210> 85

<211> 748

<212> DNA

<213> Homo sapiens

<400> 85

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tagtcatttt aaaagcaaaa tattaaattc aaagtgccta ttttctgtat tcaaaagaga 60
aaaaagtcga tctatatgac attttaatta acattttctg aaaatattta atgggattgt 120
cttctcaagt ttcttaagta atatgaactt ctattttcaa atataagcat caattttgtt 180
aaataatgta aaatctacta gcaataataa ctcatTTTTg ttgttattta ctactcttcc 240
ttgttattgt ccctccagaa cttgaagaat ctagacagaa atgtccgcca tgctggtata 300
gatttgcaa tgtgttcttg atctgggact gctgtgatgc atgggttaaaa gtaaaacatc 360
ttgtgaattt aattgttatg gatccatttg ttgatcttgc catcactatt tgcattgtct 420
taaataccct ctttatggcc atggagcact accccatgac tgagcaattc agtagtgtgt 480
tgactgtagg aaacctggtg agtacatttg aagtttactt atttactttg gtatgtgtgg 540
gagagataga ccaaagggaa agatgtattt gtgctgtgtt gaacccaaaa attatattcct 600
ctttcctcat agaaagaaat atctaaggaa tattacaggg aatctcagag atacagccta 660
aaactcaact ggtatgaatg ctgattgttt aggccaatgt ctgtgctgat tgatcatggt 720
gtcttaccag ttgtaaacgt ctcaaaat 748

```

<210> 86

<211> 664

<212> DNA

<213> Homo sapiens

<400> 86

```

ctaagacttg aattgatttg tcactattct ctcaacttta attttagata tttttattcc 60
tgtctaattg tcttctttat aaattcgtgt agcatcagtg ttttcagtg tcttgatagt 120
agtgtctgac tctaattttt taggtcttta ctgggatttt tacagcagaa atggttctca 180
agatcattgc catggatcct tattactatt tccaagaagg ctggaatata tttgatggaa 240
ttattgtcag cctcagttta atggagcttg gtctgtcaaa tgtggaggga ttgtctgtac 300
tgcgatcatt cagactggta tctatttata tatatccctg tcgctcattg gcacaacatt 360

```

```

tattttgaaa ttgaatcaat gtatatattat ataattatta attttaattt taaattttaca 420
tcaatatgtg acatttctaag aaaacatgta aacatccyct ttaaagctaa accatttttct 480
aagaatgatg aaagcattca aaatactcta taatgattag gtatgtaggg cacattagaa 540
aacctacaag tacttttctaa aactgtgttt taagtttatg aagctttttt ggccttacag 600
tctgtaaaga tacgcaaata aaaatttaga cccagttaa ttttagcttt ttattaaccc 660
tact 664

```

<210> 87

<211> 750

<212> DNA

<213> Homo sapiens

<400> 87

```

tatttttatt tttgcaactta aatgatatta tgaccagatt tacaattcta atattgttaa 60
cactattttt tctggatttg aaattgaatc agttcagtat attttgagtt ttacatcta 120
ccacgtgtgg ttctatgata ccacatacta ataaaataat gtctaaaatt atattatgat 180
tactactaac agcatctttt cacttgatta cagcttagag ttttcaagtt ggcaaaatcc 240
tggtccacac taaatatgct aattaagatc attggcaatt ctgtgggggc tctaggaaac 300
ctcaccttgg tgttgccat catcgtcttc atttttgctg tggtcggcat gcagctcttt 360
ggtaagagct acaaagaatg tgtctgcaag atcaatgatg actgtacgct cccacgggtg 420
cacatgaacg acttcttcca ctcttcctg attgtgttcc gcgtgctgtg tggagagtgg 480
atagagacca tgtgggactg tatggaggtc gctggccaaa ccatgtgcct tattgttttc 540
atgttggtca tggtcatttg aaaccttgtg gtatgtatgt agtacaaatg ctcataaatt 600
agaacaagag cagacagtag ctagggaacgt ggccagatgt agtaaacata tctctggttt 660
atagtaagtg gcctagactg aaatccccct attagcactc agagaataag caagttattt 720
aacttctcct gggctctggt ttcccatatt 750

```

<210> 88

<211> 768

<212> DNA

<213> Homo sapiens

<400> 88

```

ccttagagca ggatattagg tcctttaaag agtgtgtgac ttagacatgg catctgaaat 60
atagtaagca ttcaataaac atttgttgaa ataattttag caaagatcta tgagttccct 120
ttttaggctg ttattttaa gcatatttca atattaarat aggcattttt ctttttttct 180
tttaggttct gaacctcttt ctggccttat tgttgagttc atttagctca gacaaccttg 240
ctgctactga tgatgacaat gaaatgaata atctgcagat tgcagtagga agaatgcaaa 300
aggggaattga ttatgtgaaa aataagatgc gggagtgttt ccaaaaagcc ttttttagaa 360
agccaaaagt tatagaaatc catgaaggca ataagataga cagctgcatg tccaataata 420
ctggaattga aataagcaaa gagcttaatt atcttagaga tgggaatgga accaccagtg 480
gtgtaggtac tgggaagcagt gttgaaaaat acgtaatcga tgaaaatgat tatatgtcat 540
tcataaacia cccagcctc accgtcacag tgccaattgc tgttgagag tctgactttg 600
aaaacttaaa tactgaagag ttcagcagtg agtcagaact agaagaaagc aaggaggtaa 660
ggaatgcttt taaatttttt gttccatttc ctatgataac catgtactac agttatttac 720
tattttcatt gtgcttatat gcattatcga aaagcaatga ttgtaagt 768

```


<210> 89
 <211> 471
 <212> DNA
 <213> Homo sapiens

<400> 89
 taattattag tacataatga tcagtaatgc taatagagtt aaatgctatc actacatttt 60
 ttttcacaca atgacacagt atttcccagt tagttaaata aaagggggaa aatcacatct 120
 ttgaaatggg attttgtttc cagaaattaa atgcaaccag ctcatctgaa ggaagcacag 180
 ttgatgttgt tctaccccgga gaaggtgaac aagctgaaac tgaacccgaa gaagacctta 240
 aaccggaagc ttgttttact gaaggtaaac aagctctgat gtgattaaat acaatctccc 300
 cttgttcttt acggagactg aatatgcctc atttaaaaaa aaaaatttag caaacgaggt 360
 gtggtggctt atgcctgtaa ccccaaaatt ttgggaggct acggtaggag gattgcttga 420
 cccagaggat ttgagaccac cctgggaaat gtagtaaggc tttgcctcta c 471

<210> 90
 <211> 623
 <212> DNA
 <213> Homo sapiens

<400> 90
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 gctgacgata actaggaaat gaaggagatg gttaccctat gaaatgatta cctggaagtg 120
 gagtggggaa ggggcaagaa agtttatttt ttcctattta agattaaaat atatttttta 180
 attaactata ttttattttt aggatgtatt aaaaagtttc cattctgtca agtaagtaca 240
 gaagaaggca aagggaagat ctggtggaat cttcgaaaaa cctgctacag tattgttgag 300
 cacaactggg ttgagacttt cattgtgttc atgacccctc tcagtagtgg tgcattggta 360
 agtgaaatgc atattggcaa gaatcagatt ctggtgaaat agtttattct ccaaaattac 420
 cagatgcaaa cactgagctt cagaatcaaa agaaaaggca tatctgtgtc ttgcagagct 480
 tggcacccaa ggtttaacga tgcaaaattc agttctgaac aaatcagcac catgaaacag 540
 ccagatggaa tttctcatct ggtgtttatc taacagatgt tttcctcact gagacaacca 600
 ttgcagaga cattctgtaa cca 623

<210> 91
 <211> 520
 <212> DNA
 <213> Homo sapiens

<400> 91
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 ttattctttt gtactcacta ttataactaag caattttttc aaatatattag aagaagcaag 120
 ccatttaagt aaaataaaat atttttgatt cataggcctt tgaagatata tacattgaac 180
 agcgaaagac tatcaaaacc atgctagaat atgctgacaa agtctttacc tatatatcca 240
 ttctggaaat gcttctcaaa tgggttgctt atggatttca aacatatttc actaatgcct 300

ggtgctggct agatttcttg atcgttgatg taagtatttt aagtgatttt tataaaattg 360
 tttttaaaag aggcaagttt gacatttcat atgtttctgt tattaaaact ttcactaata 420
 atgacataat tatgcagtta tttaaacaaa actgtaacat atgcaacaat gaggaatatc 480
 tcatgggaaa gagtagagga ggtcctaaac atgggcagtg 520

<210> 92

<211> 595

<212> DNA

<213> Homo sapiens

<400> 92

ctaactaata atttaagcac acatccatga aggatctggc attgaactca atcctgaatt 60
 atcagtggtg tatgcacaag ttgaaaaggg gtccatggta taaaatatct aactggagat 120
 attgacacgt gttgataaat atgggcaagt attctggttt cattgggtta aaaaaagcaa 180
 tagtatgaga tgagactggc aatataagat gacccacta tgtggaagat gaaagttgcc 240
 aaggatgtc caaattagta tttagtctgc attaaataga taccacaccc tataccttca 300
 gtcaacagtt tatttcttgg tgaactaatt aatttttttt tccttttgta ggtttctttg 360
 gttagcctgg tagccaatgc tcttggtac tcagaactcg gtgccatcaa atcattacgg 420
 acattaagag cttaagacc tctaagagcc ttatcccggg ttgaaggcat gagggtaaga 480
 agaatagaça ctctaattat tcatgtcaaa aattacatgt aggtaatgat ttagatagaa 540
 aagggtgcca tactcttctg atatttattt caatagaaat tacagaatta gaagc 595

<210> 93

<211> 787

<212> DNA

<213> Homo sapiens

<400> 93

ccagcataca aacattttct gactccatct tactatacca ggtttttaat gatttctttt 60
 catactgtag catattttgc tttccttaaa accttagctc tttagtgtg tcattgtttg 120
 ttttccttca aatatgtgct agaaaaatta gaagaaacaa cttgtccacc tagattttta 180
 ttttaactctt ttcaagcaca tattaatact aaacaaatac attgaaggaa tggtttccat 240
 tcaaaagggtt tgtaagctat gttcccctcg ctgtctcttc taggtggttg tgaatgctct 300
 tgttgagca attccctcta tcatgaatgt gctgttggtc tgtctcatct tctggttgat 360
 ctttagcatc atgggtgtga atttgtttgc tggcaagttc taccactgtg ttaacatgac 420
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 caagcaagct cggtggaata acgtgaaagt aaactttgat aatgttggcg ctggctatct 540
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 tcaaggaaga ttatttccct gatgttcttc gtttgaatga ctaacatttg acagcatgaa 660
 aaaaagttaa tgataacacc tataatatca gcttgaattg atcataaaaa agatgttaca 720
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<210> 94

<211> 438

<212> DNA

<213> Homo sapiens

<400> 94

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tttcatctgg ttaaattgtca ttgttaggtg aaattttttat gaacaattca aatatatgtt 180
atttacaggc cacattttaa ggctggatgg atattatgta tgcagctgtt gattcacgag 240
atgtaagtat cactcaaata ttatttatag gtcttagatt tcttatggtg aatattggtg 300
gtaattttaa cactgataca tccaaaattc tatattagaa catttaatat tgcatataaa 360
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<212> DNA

<213> Homo sapiens

<400> 95

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catgtggtta ttttaagctgc agggattcca gcctctagtc agtggctcct ctcaaagttt 540
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<210> 96

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<213> Homo sapiens

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aagaattact tgtctccttt aatgttccaa agccatgcgt ccatatggtc aaattgagca 420
atgctctgga gcagaacata ttaggtgata tcaccaatat tgagccctaa ttataaagtt 480
catattttgc atcataattc acaacttctg cactcattag gagttaccac attccaaaaa 540

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aaggaggtaa tgttctttat aatttgtgag ttgaaaactt ctagctcagg gttcctaata 600.
 aatacttcca aagcaagggt cactttcctg ctaccaa 637

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<210> 98
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 <212> DNA
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<210> 99

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

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22

<210> 100

<211> 24

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 100

cttcctgctc tgcccaaact gaat

24

<210> 101

<211> 24

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

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ggcgatgtaa tgtaaggtgc tgtc

24

<210> 102

<211> 24

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
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24

<210> 103

<211> 24

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 103

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24

<210> 104

<211> 19

<212> DNA

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<223> Description of Artificial Sequence: synthetic
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tgggccattt ttcgtcgtc

19

<210> 105

<211> 25

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 105

gaaagacgca ttgcagaaga aaagg

25

<210> 106

<211> 24
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<223> Description of Artificial Sequence: synthetic
oligonucleotide

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24

<210> 107
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<223> Description of Artificial Sequence: synthetic
oligonucleotide

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25

<210> 108
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oligonucleotide

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ttcccaactt aatttgatat ttagc

25

<210> 109
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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 109

gcagtttggg cttttcaatg ttag

24.

<210> 110

<211> 24

<212> DNA

<213> Artificial Sequence

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24

<210> 111

<211> 24

<212> DNA

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oligonucleotide

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ttagggctac gtttcatttg tatg

24

<210> 112

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 112

agcactgatg gaaaaccaa ctat

24

<210> 113

<211> 24

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 113

agcccatgca gtaatataaa tcct

24

<210> 114

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 114

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24

<210> 115

<211> 22

<212> DNA

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22

<210> 116

<211> 24

<212> DNA

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oligonucleotide

<400> 116

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24

<210> 117

<211> 19

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 117

aaatacttgt gcctttgaa

19

<210> 118

<211> 23

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
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23

<210> 119

<211> 23

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 119

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23

<210> 120

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

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oligonucleotide

<400> 120

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24

<210> 121
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oligonucleotide

<400> 121
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24

<210> 122
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oligonucleotide

<400> 122
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24

<210> 123
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<400> 123
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24

<210> 124
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oligonucleotide

<400> 124

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22

<210> 125

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<212> DNA

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oligonucleotide

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gcagcaggca ggctctca

18

<210> 126

<211> 24

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<400> 126

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24

<210> 127

<211> 24

<212> DNA

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<400> 127

ataatcttgc aaaatgaaat caca

24

<210> 128

<211> 19

<212> DNA

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 128

atccgggatg acctactgg

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<210> 129

<211> 24

<212> DNA

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oligonucleotide

<400> 129

gataacgaga gccgtagaga ttcc

24

<210> 130

<211> 20

<212> DNA

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 130

agccagccat gcctgaacta

20

<210> 131

<211> 23

<212> DNA

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oligonucleotide

<400> 131

tgtttgcttg tcatattgct caa

23

<210> 132
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oligonucleotide

<400> 132
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22

<210> 133
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oligonucleotide

<400> 133
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24

<210> 134
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oligonucleotide

<400> 134
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20

<210> 135
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oligonucleotide

<400> 135
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24

<210> 136
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oligonucleotide

<400> 136
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<210> 137
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oligonucleotide

<400> 138
gcaagaaccc tgaatgtag aaa

23

<210> 139
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oligonucleotide

<400> 139

taatgctttt aagaatcata caaa

24

<210> 140

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oligonucleotide

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21

<210> 141

<211> 20

<212> DNA

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oligonucleotide

<400> 141

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20

<210> 142

<211> 22

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 142

atgtgccatg ctggtgtatt tc

22

<210> 143
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<220>
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oligonucleotide

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23

<210> 144
<211> 23
<212> DNA
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<220>
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oligonucleotide

<400> 144
cagcaatttg gagattattc att

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<210> 145
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oligonucleotide

<400> 145
gcagccactg atgatgataa

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<210> 146
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oligonucleotide

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21

<210> 147
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<400> 147
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20

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21

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19

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21

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21

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18

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24

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22

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21

<210> 168

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19

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23

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24

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23

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25

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21

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22

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17

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23

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oligonucleotide

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21

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24

<210> 184
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24

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<400> 185
caatccttc aaggtctcct atc

23

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24

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<400> 187

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22

<210> 188

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24

<210> 189

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<213> Homo sapiens

<400> 189

gcatttgaag atata

15

<210> 190

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<213> Homo sapiens

<400> 190

gcatttgacg atata

15

<210> 191

<211> 15

<212> DNA

<213> Homo sapiens

<400> 191

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15

<210> 192
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<400> 192
atcatatmct tcctg

15

<210> 193
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24

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24

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24

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24

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oligonucleotide

<400> 197
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24

<210> 198
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oligonucleotide

<400> 198
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23

<210> 199
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oligonucleotide

<400> 199
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22

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<400> 200
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<400> 202
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24

<210> 203
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<400> 203

aaggcatggt agtgcataaa ag

22

<210> 204

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<212> DNA

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<400> 204

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22

<210> 205

<211> 24

<212> DNA

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<400> 205

aatgtgagct tggctattgt ctct

24

<210> 206

<211> 23

<212> DNA

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 206

ataggctccc accagtgatt tac

23

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oligonucleotide

<400> 207
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22

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22

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19

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20

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20

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22

<210> 214
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24

<210> 215

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24

<210> 216

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24

<210> 217

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<400> 217

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18

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<400> 218
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24

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22

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23.

<210> 222

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24

<210> 223

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<210> 224

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24

<210> 226

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24

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24

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24

<210> 231

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24

<210> 232

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<400> 232

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23

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19

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24

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oligonucleotide

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21

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oligonucleotide

<400> 236

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20

<210> 237

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23

<210> 238

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24

<210> 239

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24

<210> 240

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24

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23

<210> 242

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18

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<400> 243

gtgggggctc taggaaacct

20

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24

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oligonucleotide

<400> 245
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23

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oligonucleotide

<400> 246
agtggcagca agattgtca

19

<210> 247
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oligonucleotide

<400> 247
ggccttgctt ttgagttcc 19

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oligonucleotide

<400> 248
ggtctttgcc tatttctatg gtg 23

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oligonucleotide

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oligonucleotide

<400> 250
tatacaccaa aatatctcct tat 23

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oligonucleotide

<400> 251

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24

<210> 252

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oligonucleotide

<400> 252

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24

<210> 253

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<400> 253

cccaccaaca caaatatacc taat

24

<210> 254

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22

<210> 255
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oligonucleotide

<400> 255
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22

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oligonucleotide

<400> 256
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24

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oligonucleotide

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24

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oligonucleotide

<400> 258

tgacatttcc atggtacaaa gtgt

24

<210> 259

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oligonucleotide

<400> 259

tttgttggtg gcttttcact tat

23

<210> 260

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oligonucleotide

<400> 260

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19

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

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taagcgtggt caacaactac agt

23

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 262

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22

<210> 263

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oligonucleotide

<400> 263

caaaacattg ccccaaaag

19

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oligonucleotide

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24

<210> 265

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<223> Description of Artificial Sequence: synthetic
oligonucleotide

<400> 265

gataattaaa aactcactga tgta

24

<210> 266

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23

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24

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24

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9

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9

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9

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20

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24

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24

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23

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22

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21

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20

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23.

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23

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24

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24

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22

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oligonucleotide

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24

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24

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23

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19

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20

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22

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24

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oligonucleotide

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22

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23

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23

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oligonucleotide

<400> 354
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24

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<400> 355

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18

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<400> 356

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22

<210> 357

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20

<210> 358

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20

<210> 359

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23

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24

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<400> 362

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22

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oligonucleotide

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21

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oligonucleotide

<400> 364
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21

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oligonucleotide

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23

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oligonucleotide

<400> 366
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21

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oligonucleotide

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24

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19

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24

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26

<210> 371

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24

<210> 372

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taccacaccc tataccttca gtca

24

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<400> 373

gagtatggca cccttttcta tcta

24

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oligonucleotide

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gctatgttcc cctcgctgtc t

21

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oligonucleotide

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19

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oligonucleotide

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22

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oligonucleotide

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caaacgaaga acatcagggg aata

24

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24

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23

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24

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22

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<210> 391
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<210> 393

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23

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<210> 396

<211> 23

<212> DNA

<213> Artificial Sequence

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<210> 397

<211> 24

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<210> 398

<211> 23

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<210> 399

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<213> Homo sapiens

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<400> 402
tggtgtaagg tag

13

<210> 403
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<400> 403
tggtataagg tag

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<400> 405
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15

<210> 408
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<212> DNA
<213> Homo sapiens

<400> 408
aaatacrtaa tcgat

15

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60/167.623 26 November 1999 (26.11.1999) **US**
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY, MUTATIONS THEREOF AND METHOD USING SAME TO ASSESS, DIAGNOSE, PROGNOSIS OR TREAT EPILEPSY**

(57) Abstract: The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three genes mapping to chromosome 2, which show mutations in patients with epilepsy. The invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA) and to the use thereof to assess, diagnose, prognosis or treat epilepsy, to predict an epileptic individual's response to medication and to identify agents which modulate the function of the SCNA. The invention provides screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders. In a particular embodiment, the invention provides a method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising: providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting this screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene; wherein a test compound which modulates the biological activity thereof is a compound with the desired therapeutic effect.

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INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 A61P43/00 C07K14/705

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOULARD BRUNO ET AL: "Identification of a new locus for generalized epilepsy with febrile seizures plus (GEFS+) on chromosome 2q24-q33." AMERICAN JOURNAL OF HUMAN GENETICS, vol. 65, no. 5, November 1999 (1999-11), pages 1396-1400, XP002170644 ISSN: 0002-9297 the whole document	1-13
X	BAULAC S ET AL: "A second locus for familial generalized epilepsy with febrile seizures plus maps to chromosome 2q21-q33." AMERICAN JOURNAL OF HUMAN GENETICS, (1999 OCT) 65 (4) 1078-85. , XP002170645 the whole document	1-13

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

27 June 2001

Date of mailing of the international search report

11/07/2001

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01404

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>PUGSLEY MICHAEL K ET AL: "Effects of bisaramil, a novel class I antiarrhythmic agent, on heart, skeletal muscle and brain Na⁺ channels."</p> <p>EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 342, no. 1, 19 January 1998 (1998-01-19), pages 93-104, XP001009949 ISSN: 0014-2999 the whole document</p>	12,13
A	<p>WALLACE ROBYN H ET AL: "Febrile seizures and generalized epilepsy associated with a mutation in the Na⁺-channel beta1 subunit gene SCN1B."</p> <p>NATURE GENETICS, vol. 19, no. 4, August 1998 (1998-08), pages 366-370, XP001009923 ISSN: 1061-4036 cited in the application the whole document</p>	1-13
A	<p>MALO M S ET AL: "TARGETED GENE WALKING BY LOW STRINGENCY POLYMERASE CHAIN REACTION: ASSIGNMENT OF A PUTATIVE HUMAN BRAIN SODIUM CHANNEL GENE (SCN3A) TO CHROMOSOME 2Q24-31"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 91, no. 8, 12 April 1994 (1994-04-12), pages 2975-2979, XP002051362 ISSN: 0027-8424 the whole document</p>	1-13
A	<p>MALO M S ET AL: "LOCALIZATION OF A PUTATIVE HUMAN BRAIN SODIUM CHANNEL GENE (SCN1A) TO CHROMOSOME BAND 2Q24"</p> <p>CYTOGENETICS AND CELL GENETICS,CH,BASEL, vol. 67, no. 3, 1994, pages 178-186, XP000603748 ISSN: 0301-0171 the whole document</p>	1-13
A	<p>PLUMMER NICHOLAS W ET AL: "Evolution and diversity of mammalian sodium channel genes."</p> <p>GENOMICS, vol. 57, no. 2, 15 April 1999 (1999-04-15), pages 323-331, XP002170646 ISSN: 0888-7543 the whole document</p>	1-13

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/01404

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 21875 A (UNIV UTAH RES FOUND) 6 May 1999 (1999-05-06) the whole document	1-13
P,X	----- ESCAYG ANDREW ET AL: "Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS+2." NATURE GENETICS, vol. 24, no. 4, April 2000 (2000-04), pages 343-345, XP001009967 ISSN: 1061-4036 cited in the application the whole document -----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 00/01404

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921875 A	06-05-1999	EP 1037900 A	27-09-2000